World Health Organization Classification of Tumours

International Agency for Research on Cancer (IARC)

Pathology and Genetics of Skin Tumours

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Keratinocytic Tumours

Keratinocytic tumours are derived from epidermal and adnexal keratinocytes and comprise a large spectrum of lesions ranging from benign proliferations (acanthomas) to malignant squamous cell carcinomas which occasionally show aggressive growth and even metastatic potential. Keratinocytic tumours are very frequent and, despite their low mortality rate, pose a significant public health problem. The main etiologic factor is solar radiation which causes DNA alterations, including pyrimidine dimers which during DNA replication may lead to CC:TT mutations in the \textit{TP53} tumour suppressor gene. Other genes involved in the multistep formation of skin cancer include \textit{PTCH} and the \textit{RAS} oncogene. Verrucas, epidermal proliferations produced by infection with human papilloma viruses (HPV), are also included in this section.
WHO histological classification of keratinocytic skin tumours

### Keratinocytic tumours

<table>
<thead>
<tr>
<th>Description</th>
<th>Code</th>
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<tr>
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<tr>
<td>Superficial basal cell carcinoma</td>
<td>8091/3</td>
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<td>Nodular (solid) basal cell carcinoma</td>
<td>8097/3</td>
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<td>Infiltrating basal cell carcinoma</td>
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<td>Fibroepithelial basal cell carcinoma</td>
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<td>Basal cell carcinoma with adnexal differentiation</td>
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<td>8094/3</td>
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<td>Keratotic basal cell carcinoma</td>
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<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
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<td>Bowen disease</td>
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<td>Bowenoid papulosis</td>
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<td>Actinic keratosis</td>
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<td>Keratoacanthoma</td>
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<tr>
<td>Lichen planus-like keratosis</td>
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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (786) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for in situ carcinoma and /1 for borderline or uncertain behaviour.

### TNM classification of skin carcinomas

#### TNM classification

**T - Primary tumour**

- **TX**: Primary tumour cannot be assessed
- **T0**: No evidence of primary tumour
- **Tis**: Carcinoma in situ
- **T1**: Tumour 2 cm or less in greatest dimension
- **T2**: Tumour more than 2 cm but no more than 5 cm in greatest dimension
- **T3**: Tumour more than 5 cm in greatest dimension
- **T4**: Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

**N - Regional lymph nodes**

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

**M - Distant metastasis**

- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis

**Stage grouping**

- Stage I: T1, Tis, N0
- Stage II: T2, T3, N0
- Stage III: T4, Any T, N1
- Stage IV: Any T, Any N

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

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1. (784,2219).
The keratinocytic tumours are a clinically and histopathologically diverse group of lesions derived from the proliferation of epidermal and adnexal keratinocytes. At one end of the spectrum the proliferations are benign (acanthomas) and usually of cosmetic importance only, while at the other there are malignant tumours, which uncommonly may be aggressive with metastatic potential, as seen with some squamous cell carcinomas. Included in the spectrum are the epidermal dysplasias (actinic keratosis, arsenical keratosis and PUVA keratosis) and intraepidermal carcinomas (Bowen disease and bowenoid papulosis). Ackerman and others have proposed that solar keratoses should be regarded as squamous cell carcinoma de novo and not as pre-malignancies or pre-cancers that evolve into squamous cell carcinoma (994,1443,1701).

Epidemiology
Keratinocytic tumours are an important public health problem, despite their comparatively low mortality rate (2484). The lifetime risk for the development of skin cancer in the USA is now 1 in 5 (1937). It is much higher in subtropical Australia. There is an increasing incidence of squamous cell carcinoma of the skin in some countries (2462). Keratinocytic tumours account for approximately 90% or more of all skin malignancies, of which approximately 70% are basal cell carcinomas. The latter exceed squamous cell carcinomas in frequency by a factor of approximately 5:1 although in lower latitudes the incidence of squamous cell carcinoma increases and this ratio becomes 3:1. If solar keratoses are regarded as squamous cell carcinomas (see above), then squamous cell carcinoma becomes the more common tumour (300).

Precursor lesions
There are no known precursor lesions to basal cell carcinoma. On the other hand, there are a number of intra-epidermal proliferative disorders (dysplasias) that may be precursors of squamous cell carcinoma. These include actinic keratoses and Bowen disease (intraepidermal carcinoma/squamous cell carcinoma in-situ).

Actinic keratoses are erythematous, scaling lesions occurring on heavily sunlight exposed areas that increase in prevalence with increasing age in fair skinned people. Histologically, they demonstrate confluent keratinocytic atypia involving predominantly the keratinocytes in the basal layer of the epidermis (2475).

It is difficult to determine the incidence of actinic keratoses as they come and go over time (788). Longitudinal studies suggest that they are likely to be a precursor of squamous cell carcinoma, although the malignant transformation rate is small, certainly less than one in a hundred per year (1517). Data suggest, also, that remission of these lesions will occur if sunlight exposure can be reduced. Thus the majority of lesions do not progress to squamous cell carcinoma (1516,2349).

Bowen disease demonstrates keratinocyte atypia involving the full thickness of the epidermis. There is also involvement of the hair follicle and rarely the sweat duct. Although Bowen disease has been classified as a full thickness in-situ squamous cell carcinoma, there are no longitudinal studies published on the frequency of malignant transformation. Even if invasive squamous cell carcinoma does occur within one of these lesions, it is believed that the in-situ phase may be very prolonged, lasting many years (1203).

Etiology
Findings regarding the genetic basis of non-melanoma skin cancer (NMSC) have confirmed that UV radiation, especially UVB (290-320 nm in the solar spectrum), contributes to the formation of squamous (1336) and basal cell carcinomas (602). Squamous cell carcinomas (SCCs) of the skin develop through a multistep process that involves activation of proto-oncogenes and/or inactivation of tumour suppressor genes in the human skin keratinocytes. NMSCs are caused by genetic abnormalities, most often induced by UVB exposure. Actinic keratoses, which lead to SCCs, have gene mutations in K-ras (2235). H-rasV12 and cyclin dependent kinase 4 (CDK4) produce human epidermal neoplasia. Therefore, a combination of these genetic abnormalities might be crucial to the carcinogenesis at least in a subset of SCCs (1336).

High doses of ultraviolet light can also lead to skin cancers by inducing reactive oxygen species (ROS) that play an important role in tissue injury. Increased production of ROS and/or decreased efficiency of antioxidant defence system contribute to a number of degenerative processes including cancer (1161). UV induces pyrimidine dimers and loss of heterozygosity (LOH). TP53 and PTCH, two tumour suppressor genes, have LOH which lead to basal cell carcinoma (BCC) (1265). LOH in TP53 is related to elevated microsatellite instability at selected tetranucleotide repeats (587). LOH at 9q22 loci in PTCH genes causes non-melanoma skin cancer tumours (1265). The type of mutations for TP53 and PTCH are predominantly UV-signature transitions, C->T and CC->TT at dipyrimidine sites (1265). SCCs have mutations of H-Ras gene and the INK4a locus whereas BCC has missense mutations leading to rasGTPase activating protein (168). Further, mutations have been found in both TP53 tumour suppressor gene and ras in patients with xeroderma pigmentosum (XP), a disease of DNA repair deficiencies (1717). Common exogenous carcinogenic agents in addition to UV radiation include 1) tobacco use (2457), 2) human papilloma viruses (1703), 3) arsenic (2184), 4) industrial chemicals such as vinyl chloride (1362), polycyclic aromatic hydrocarbons (1086), 5) MNNG (N-methyl-N-nitro-N-nitrosoguanidine), an alkylating agent (335), and 6) exposure to gasoline or gasoline vapours (1567).
Clinical features
Keratinocytic tumours vary in their clinical appearance depending on the type of lesion and stage of development.

Histopathology
The histopathologic changes noted in keratinocytic proliferative lesions involve disturbance of normal surface maturation. The degree and extent of keratinocytic atypia vary in these lesions. The atypical keratinocytes show enlarged nuclei with hyperchromasia, dyskeratosis and mitoses in any layer of the epithelium. In lesions of epidermal dysplasias (AK, arsenical, and PUVA keratoses), surface keratinocytic maturation is present, i.e. a granular cell layer is usually noted.

In intraepidermal carcinomas (Bowen disease, bowenoid papulosis), there is full-thickness involvement of the epidermis by the atypical keratinocytes.

Molecular markers
A number of potentially useful molecular markers or tests have been proposed. These include the demonstration of a different pattern of basic fibroblast growth factor expression in neoplastic keratinocytes by in situ hybridization and the persistence of integrated HPV sequences in the host cell genome of HPV associated keratinocytic lesions detected by ligation mediated PCR assay. The lower level of TIG-3 mRNA expression in SCC is visualized by immunohistochemistry or by in situ mRNA hybridization. Upregulation of S100 protein subtypes in specific keratinocyte disorders is confirmed by immunohistochemistry.

Prognosis and predictive factors
Most patients with primary cutaneous non-melanoma skin cancer (NMSC) have an excellent prognosis. The overall mortality rates are generally low, on average approximately 0.1% of the incidence rates, but significantly higher for SCCs than BCCs. Invasive SCC has the potential to recur and metastasize with an overall 5-year rate of recurrence for primary tumours of 8%. With the exception of lip tumours, squamous cell carcinomas arising in actinic keratoses have a frequency of metastatic spread of 0.5-3% (1459,1630). For those with metastatic disease the long-term prognosis is poor; 10-year survival rates are <20% for patients with regional lymph node involvement and <10% for patients with distant metastases (50). More than 70% of SCC recurrences and metastases develop within 2 years of treatment of the primary tumour (635), and 95% within 5 years (1985). The 3-year cumulative risk of non-melanoma skin cancer developing in an individual diagnosed with SCC is 35-60% and the risk of melanoma is also increased (1507). Five-year cure rates for BCC of up to 99% are obtainable with surgical techniques (1617, 1984), and metastasis is extremely rare, occurring in approximately 0.05% of cases (1440). As with SCC, patients with BCC are at high risk of further primary BCCs; in patients with one lesion the 5-year risk is 27%, and in those with 10 lesions the risk is 90% (1208), and the risk of SCC and malignant melanoma is also increased (1208,1430).
Definition
A group of malignant cutaneous tumours characterised by the presence of lobules, columns, bands or cords of basaloid cells (“germinative cells”).

ICD-O code 8090/3

Synonyms
Basal cell epithelioma, trichoblastic carcinoma.

Epidemiology
Basal cell carcinomas (BCC) develop predominantly in sun-damaged skin in individuals who are fair skinned and prone to sunburn (330,888,889). Migration of such individuals particularly as children, to countries with high UV radiance is associated with increased rates of skin cancer. Although basal cell carcinomas typically occur in adults, the tumours also develop in children (1873). Arsenic exposure (924) and ionizing radiation may also induce basal cell carcinomas.

Nodular basal cell carcinomas occur at a later age than superficial basal cell carcinomas and are more frequently on the head whereas the trunk is the most frequent site for superficial tumours (1550, 2121).

Basal cell carcinomas are very frequent tumours particularly in light-skinned individuals living in countries at low latitudes. Incidences of 2000 per 100,000 population have been recorded in Queensland, Australia. The rate of basal cell carcinomas has increased in the older age groups. Older men have a higher incidence of basal cell carcinoma than women, but women have been found to outnumber men in younger age groups. The latter may be due to increased sun exposure in younger women in association with tanning bed use as well as smoking (293).

Clinical features
Basal cell carcinomas typically have a pearly appearance with telangiectasia that may appear as a papule or nodule that can be eroded or ulcerated. These features may be more subtle in the superficial forms that appear as erythematous patches resembling an area of dermatitis. Pale scar-like lesions may also be a presentation of basal cell carcinoma and these slowly grow over years. Pigmented basal cell carcinomas may masquerade as melanomas but usually can be distinguished by the presence of a pearly component. Dermatoscopy is also helpful in analysing pigmented basal cell carcinoma and distinguishing these from melanocytic tumours (1587). Erosive lesions on the lower limbs may be mistaken for slowly healing traumatic wounds. Delays in clinical diagnosis may occur for basal cell carcinomas that are localized within non-sun exposed sites (225) such as the perianal area (1312) or between the toes, young age of onset, tumours with very slow growth, or superficial erythematous patches that appear as a dermatitis or tumours complicating vaccination scars, rhinophyma or a venous ulcer. The clinical capacity to differentiate some basal cell carcinomas from squamous cell carcinoma or even melanoma may be impossible without skin biopsy. In countries with a high incidence of basal cell carcinomas it is not unusual to have individuals with multiple basal cell carcinomas, and regular review is required to deal with new skin tumours. Incomplete removal of basal cell carcinoma may result in delayed recurrences that may not be recognized for years, particularly if the tumour recurrence is deep or masked by skin grafts.

Genetics
Genetic analysis of sporadic basal cell carcinoma (2024) has been propelled by the identification of mutations in PTCH1 (chromosome 9q22.3) as the cause of the basal cell nevus syndrome (BCNS), a rare autosomal dominant disorder (110, 1146,2395). These patients develop multiple basal cell carcinomas which may appear in childhood (see Chapter 2). PTCH1 encodes a protein that functions as an inhibitor of the hedgehog signaling pathway, and BCCs, whether sporadic or occurring in BCNS patients, all have abnormalities of this signaling pathway (110,1146,2272,2395). In most sporadic BCCs this is due to somatically-acquired mutations in PTCH1 (802), and in many
tumours the type of PTCH1 mutations are those expected from UV-mutagenesis (108,1265). Approximately 10% of sporadic BCCs have mutations in SMOOTHENED which encodes the protein whose function is inhibited by the PATCHED1 protein (2553). Thus it appears that the relevant dysfunction driving BCCs is abnormal hedgehog signaling, irrespective of which gene controlling that signaling is mutated. The identification of hedgehog signaling abnormalities as crucial to BCC formation has stimulated the development of genetically-engineered mice with hedgehog signaling abnormalities as crucial to BCC formation has stimulated the development of genetically-engineered mice with hedgehog signaling abnormalities (109,708,1716,2163). Unlike previously studied mouse carcinogenesis models, which uniformly produce tumours of the squamous cell lineage, these mice develop BCCs and either spontaneously or in response to environmental mutagens (i.e. UV or ionizing radiation) develop BCCs and adnexal basaloid tumours.

**Histopathology**

The multiple variants of basal cell carcinoma are connected by the common histological feature of lobules, columns, bands and cords of basaloid cells (“germinative cells”) associated with scant cytoplasm and a characteristic outer palisade of cells associated with a surrounding loose fibromucinous stroma (2147,2282). Artefactual retraction spaces between the tumour and stroma are often present. The tumour-stromal interaction is weakened by the characteristic lack of the hemidesmosomes that anchor the normal epidermis to the dermis (475). Apoptosis is usually apparent. The release of keratin into the stroma as a result of apoptosis may lead to the formation of amyloid deposits (2067). Mucinous cystic degeneration, focal vacuolation with lipid or ductular differentiation, and in rare cases, sebocytes or follicular differentiation with squamous eddies, trichohyaline granules and blue-grey corneocytes may be seen. Melanocytes may proliferate within some tumours and produce pigmentation by melanin production that can be stored in tumour cells or in surrounding melanophages (1365). Problematic lesions include tumours that merge with squamous cell carcinoma (basaloid squamous cell carcinoma) or those that share adnexal differentiation demonstrating trichilemmal or seba-
some examples of morpheic or sclerotic basal cell carcinoma may resemble desmoplastic trichoepithelioma or microcystic adnexal carcinoma particularly when a small sample is obtained for analysis. The growth pattern of the basal cell carcinoma should be included in the pathology report as well as the presence of perineural involvement and excision margins particularly if less than 1 mm. Although the majority of basal cell carcinomas can be classified into the nodular, micronodular, superficial, sclerosing/morpheic or infiltrative subtypes, it is not unusual to have a mixed pattern.

**Immunoprofile**
Occasionally in curette specimens, differentiation from small cell melanoma may require the use of a combination of light-weight keratin markers and S100 acidic protein to differentiate the tumours. BerEP4, a keratin marker, has been used to differentiate basal cell carcinoma from squamous cell carcinomas (2334). CK20, a marker for Merkel cells, has been used to differentiate some forms of trichoblastoma, trichoepithelioma or fibroepitheliomas as these have scattered CK20 positive Merkel cells compared to basal cell carcinoma where they are rare or absent (13,2104).

**Prognosis and predictive factors**
Basal cell carcinomas are locally invasive tumours and metastases occur in less than 1 in 10,000 tumours (1440, 1950,2443). Morbidity is increased with deeply invasive tumours which may extend into the deep tissue to bone and follow fusion planes particularly on the face where they follow nerves through bony channels. Morbidity also increases with neglected tumours that may measure more than 10 cm in diameter and have been described as giant basal cell carcinomas (1502,2009). Multiple recurrences with deep residual tumour on the head may be associated with particular morbidity as basal cell carcinomas can ultimately penetrate the cranium. Increased recurrences are associated with infiltrative, morpheic and micronodular basal cell carcinomas as surgical margins may be underestimated (639, 1940). The possibility of the BCNS should be considered in children who develop BCCs. Families can be screened for mutations of the PTCH1 gene. Low bcl-2 protein expression has been found to correlate with clinically aggressive basal cell carcinomas with infiltrative, sclerosing/morpheic patterns as compared to superficial and nodular tumours (296,1883). BCC recurrences are more common in lesions on the nose and nasolabial fold, but this may be in part due to the difficulty in achieving adequate margins in these sites (638,651). Tumours recurring after radiotherapy are usually aggressive and infiltrative (2209). Lesions which metastasize are usually large, ulcerated, deeply infiltrating and recurrent (70). The risk of further primary BCCs is increased by male gender, age over 60 years and truncal site (1208,1378). Rarely, extensive perineural invasion is seen in infiltrative primary BCCs of the face, presenting life-threatening complications of CNS extension (317,946). Distance to the closest resection margin is an important predictor of BCC recurrence (639).

**Superficial basal cell carcinoma**

**ICD-O code** 8091/3

**Clinical features**
This variant appears as erythematous patches that are often multiple and may vary from a few millimetres to over 10 cm in diameter. A fine pearly border or central superficial erosions with a history of contact bleeding may be present. Areas of regression may appear as pale patches or fibrosis. This variant makes up 10-30% of basal cell carcinomas and occurs most frequently on the trunk.

**Histopathology**
The histopathology consists of superficial lobules of basaloïd cells which project from the epidermis or from the sides of follicles or eccrine ducts into the dermis and are surrounded by loose myxoid stroma. The lobules are usually confined
to the papillary dermis. Some examples of superficial basal cell carcinoma appear multifocal on vertical sections but may be connected by a stroma when reconstructed by three-dimensional techniques using digital image analysis. There are, however, examples of multifocal superficial basal cell carcinoma where the lobules are separated by large distances and represent discrete tumours that are truly multifocal and may measure only a few millimetres in diameter. Mixed patterns with a nodular, micronodular or infiltrative component may be seen in some tumours.

**Nodular basal cell carcinoma**

*ICD-O code* 8097/3

*Clinical features*

Nodular (solid) basal cell carcinomas often appear as elevated pearly nodules associated with telangiectasia but may become ulcerated or cystic. Endophytic nodules may present as flat indurated lesions. Haemorrhagic lesions may resemble haemangiomas or melanoma when pigmented. Nodular basal cell carcinomas make up 60-80% of tumours and occur most frequently on the head.

*Histopathology*

Histopathology shows large lobules of basaloid cells ("germinative cells") with peripheral palisading nuclei that project into the reticular dermis or deeper. The lobules may have associated mucinous degeneration with cysts or have an adenoid (cribriform) pattern. Some nodules may have an organoid appearance with smaller basaloid lobules that are connected by loose fibromucinous stroma. The periphery of such nodules should be scanned to ensure that an outlying micronodular pattern has not developed.

**Micronodular basal cell carcinoma**

*ICD-O code* 8090/3

*Clinical features*

Micronodular basal cell carcinoma presents as elevated or flat infiltrative tumours. The most common site is the back.

*Histopathology*

Histopathology shows large lobules of basaloid cells ("germinative cells") with peripheral palisading nuclei that project into the reticular dermis or deeper. The lobules may have associated mucinous degeneration with cysts or have an adenoid (cribriform) pattern. Some nodules may have an organoid appearance with smaller basaloid lobules that are connected by loose fibromucinous stroma. The periphery of such nodules should be scanned to ensure that an outlying micronodular pattern has not developed.
**Infiltrating basal cell carcinoma**

**Definition**
This variant of BCC is composed of thin strands, cords and columns of basaloid cells that infiltrate between the collagen bundles of the dermis and may extend into deeper tissues.

**ICD-O code** 8092/3

**Clinical features**
The infiltrative basal cell carcinoma presents as a pale, indurated poorly-defined plaque. These tumours are usually found on the upper trunk or face. Paraesthesia or loss of sensation may develop rarely as a manifestation of perineural extension, particularly in lesions on the face. This variant is important in that the margins at the time of surgery may be frequently underestimated.

**Histopathology**
Infiltrative patterns of basal cell carcinoma appear as strands, cords and columns of basaloid cells with scant cytoplasm. Peripheral palisading and retraction spaces are usually not seen. There is no fibrosis/sclerosis as seen in the sclerosing/morpheic variant. The infiltrative pattern is particularly associated with perineural invasion. Low molecular-weight keratin markers are useful in highlighting subtle groups of tumour cells (that may consist of 1-2 keratinocytes on cross section), in assessing clearance of the tumour and in confirming perineural involvement.

**Differential diagnosis**
Due to the cord-like arrangement of this variant there is a morphological overlap with the tumour pattern seen in microcystic adnexal carcinoma (sclerosing sweat duct carcinoma), desmoplastic squamous cell carcinoma and desmoplastic trichoepithelioma.

**Fibroepithelial basal cell carcinoma**

**Definition**
This variant of BCC is characterised by a unique clinicopathological presentation and an indolent behaviour.

**ICD-O code** 8093/3

**Synonyms**
Fibroepithelioma of Pinkus, Pinkus tumour

**Clinical features**
These tumours usually appear as an elevated flesh coloured or erythematous nodule that may resemble a seborrhoeic keratosis or acrochordon. The lesions are most often found on the back and are rarely multiple (1834). Prior radiotherapy may predispose to these tumours.

**Histopathology**
The histopathology is characterised by an arborising network of cords of basaloid cells that extend downwards from the epidermis and create a fenestrating pattern. There are strands of basaloid cells that surround fibrovascular stroma. Ductules may be present in some of the cords which may represent extension of the tumour down pre-existing eccrine ducts (2263). The cords also are associated with small follicle-like bulbs which project into the surrounding connective tissue.

**Histogenesis**
Fibroepitheliomas, like BCCs, may be best classified as a form of appendageal tumour. These tumours have mutations of the PTCH1 gene. In some fibroepitheliomas transition to classical basal cell carcinomas may be seen, and this conversion may reflect a further mutation. A variant of fibroepithelioma with extramammary Paget’s cells has been described in the perianal area (2461).
Basal cell carcinoma with adnexal differentiation

Definition
This variant is characterized histologically by adnexal differentiation in a BCC.

ICD-O code 8098/3

Clinical features
This variant has no distinguishing clinical features.

Histopathology
This variant is characterized by the presence of adnexal differentiation including basaloid buds, ductal, sebaceous and trichilemmal elements. Follicular differentiation may be prominent in more superficial BCCs. Eccrine or apocrine differentiation has also been observed in some basal cell carcinomas (997,2022). It is important to distinguish such tumours from sweat gland carcinomas which have an increased risk for metastases. Some forms of adnexal basal cell carcinomas show overlap and may be better classified as benign adnexal tumour such as a basaloid follicular hamartoma, trichoepithelioma, trichoblastoma or trichilemmoma.

Histogenesis
The cytokeratin profile of basal cell carcinoma is essentially identical to that of trichoblastomas (immature trichoepithelioma) and developing fetal hair follicles linking all basal cell carcinomas to the pilosebaceous pathway of differentiation (2086). It has been proposed that basal cell carcinoma be renamed trichoblastic carcinoma (1623).

Prognosis and predictive factors
These patterns of adnexal differentiation do not appear to have any prognostic implications.

Basosquamous carcinoma

Definition
Basosquamous carcinoma is a term used to describe basal cell carcinomas that are associated with squamous differentiation (285,2102).

ICD-O code 8094/3

Synonyms
Metatypical carcinoma, basosquamous cell carcinoma

Clinical features
This variant has no distinguishing clinical features.

Histopathology
The tumour cells have more abundant cytoplasm with more marked keratinization than typical basal cell carcinomas. The nuclei have vesicular chromatin with pleomorphism and palisading may be focally lost. Some examples of this variant may merge with sebaceous carcinoma as lipid vacuoles or ducts may be focally apparent. This tumour may also have central fibrosis and a radiating peripheral rim of infiltrative cells extending into the deep dermis or subcutis.

Prognosis and predictive factors
This variant has a more aggressive behaviour and has been associated with regional or widespread metastases (1525).
Keratotic basal cell carcinoma

Definition
This variant is characterized by the presence of prominent keratin formation (horn cysts) in the centre of tumour islands.

ICD-O code 8090/3

Clinical features
This variant characteristically appears pearly and may be studded with small keratin cysts (milia).

Histopathology
These tumours share the overall architectural features of a nodular BCC. Keratinization may be laminated and infundibular in type or hyaline and trichilemmal in type or consist of keratinised shadow cells representing pilomatricetal differentiation (66). Dystrophic calcification is frequently present. Trichilemmal keratin may be associated with accentuated apoptosis in surrounding tumour cells and the presence of pale keratinocytes.

Differential diagnosis
This variant is distinguished from basosquamous carcinoma by the presence of numerous, superficial small keratin cysts. Basosquamous carcinoma is usually larger and less well circumscribed.

Other variants
Other variants account for less than 10% of all basal cell carcinomas. Many of them do not have distinctive clinical features.

Cystic
One or more cystic spaces, of variable size, are present near the centre of the tumour nests. There is sometimes increased mucin between the cells bordering the central space (2112).

Adenoid
There are thin strands of basaloïd cells in a reticulate pattern. Stromal mucin is often present. The adenoid type may occur in association with the nodular (solid) type.

Sclerosing / morpheiform
Strands and nests of tumour cells are embedded in a dense fibrous stroma (1932). Some authors use the term morpheic for any BCC with a fibrous stroma, while others restrict it to those BCC’s with keloidal collagen bundles in the stroma (1923). Enhanced procollagen gene expression has been found in this variant (1657). Furthermore, smooth muscle α-actin is often present in the stroma. This variant usually presents as an indurated, pale plaque with a slightly shiny surface and indistinct margins.

Infundibulocystic
Often confused with the keratotic type, this variant is composed of small infundibular-like structures with a central keratinous plug and a peripheral component of basaloïd cells (1218). The nests are arranged in an anastomosing pattern. Multiple lesions are sometimes present (1178).

Pigmented
Pigmentation may occur in several of the variants including the nodular, micronodular, multifocal superficial and keratotic types. Melanocytes are scattered through the tumour nests, while melanophages are present in the stroma (1495). This variant can be misdiagnosed clinically as malignant melanoma.

Miscellaneous
Other rare variants, subject to isolated case reports, include the clear-cell (165), "signet-ring"-cell (1269,2503), granular-cell (1659) and giant ("monster")-cell (880) types. Adamantanoid (1403), neuroendocrine (817) and schwannoid (2032) variants have also been described.
Squamous cell carcinoma

Definition
Squamous cell carcinoma is a malignant neoplasm of epidermal (and mucous membrane) keratinocytes in which the component cells show variable squamous differentiation.

ICD-O code 8070/3

Epidemiology
Most cases arise on the sun-exposed skin of elderly people. They can occur on all cutaneous surfaces and mucous membranes, and in younger patients, especially those with a fair complexion who tan poorly. Its incidence in an Australian study was 166 cases per 100,000 of the population, the highest in the world [828]. It is relatively uncommon in Black people.

Etiology
Ultraviolet-B radiation is the most important etiological factor. Less important factors include radiation therapy, previous burns, arsenic, coal tar [1759]; industrial carcinogens, immunosuppression, HPV infection, and inflammatory lesions and ulcers of long standing (see Introduction). Organ transplant recipients are particularly prone to develop these tumours. Most of the fatal cases have been reported from Australia, suggesting that sunlight, which also has a profound effect on the cutaneous immune system plays a role in the formation of these aggressive tumours [1974]. HPV infection is commonly found in these immunosuppressed patients [264].

Localization
Most SCCs arise in areas of direct exposure to the sun, such as the forehead, face, ears, scalp, neck and dorsum of the hands. The vermilion part of the lower lip is another common site.

Clinical features
Squamous cell carcinomas present as shallow ulcers, often with a keratinous crust and elevated, indurated surrounds, or as plaques or nodules. The surrounding skin usually shows changes of actinic damage.

Histopathology
Squamous cell carcinoma consists of nests, sheets and strands of squamous epithelial cells which arise from the epidermis and extend into the dermis for a variable distance. The cells have abundant eosinophilic cytoplasm and a large, often vesicular, nucleus. There are prominent intercellular bridges. There is variable central keratinization and horn pearl formation, depending on the differentiation of the tumour.

The degree of anaplasia in the tumour nests is used to grade the tumours. A rather subjective assessment is usually made using the categories of 'well,' ‘moderately’ and ‘poorly’ differentiated. Most squamous cell carcinomas arise in solar keratoses and evidence of this lesion is usually present at the periphery of the invasive tumour.

Squamous cell carcinomas occasionally infiltrate along nerve sheaths, the adventitia of blood vessels, lymphatics, fascial planes and embryological fusion plates [218]. The presence of perineural lymphocytes is a clue to the likely presence of perineural invasion in deeper sections [2289].

There may be a mild to moderate chronic inflammatory cell infiltrate at the periphery of the tumours. This infiltrate sometimes includes eosinophils [1455]. Rare histological variants of SCC include clear-cell [1344], signet-ring [1557], pigmentated [451], basaloid [573], inflammatory, infiltrative [1395], desmoplastic [1546] and rhabdoid [1534] types. The cells in SCC are positive for epithelial membrane antigen and cytokeratin. The keratins are of higher molecular weight than those found in basal cell carcinoma [1672].

Prognosis and predictive factors
The majority of squamous cell carcinomas are only locally aggressive and are cured by several different modalities [1656]. SCC developing in patients who are immunocompromised (including those infected with the human immunodeficiency virus [1704], are usually more aggressive. Tumours with deep invasion, poor differentiation, perineural invasion and acantholytic features are more likely to recur or metastasize. Narrow surgical margins are another risk factor for recurrence [2389].

The clinical setting in which the SCC arises also influences the risk of metastasis. Tumours arising in sun-damaged skin have the lowest risk, in the order of 0.5% or less, while for those arising in skin not exposed to the sun, the risk is 2-3%. The risk is further increased for tumours arising in Bowen disease [1203], on the lip, vulvar, perineal and penile skin and in a Marjolin ulcer, radiation scar or thermal burn. Tumour thickness is a prognostic variable, just as it is for melanoma. SCCs less than 2 mm in thickness rarely metastasize, while those between 2 and 5 mm thick are of intermediate risk (about 5%). Tumours greater than 5 mm in thickness have a risk of metastasis of about 20% [1254]. Tumours greater than 2 cm in diameter are more likely to recur and metastasize than smaller lesions [1985].

Fig. 1.12 Squamous cell carcinoma in an elderly male with delayed medical treatment. This is an unusually large neoplasm which spread to the regional lymph nodes.
**Acantholytic squamous cell carcinoma**

**Definition**
Acantholytic squamous cell carcinoma (ASCC) is a histologic variant of cutaneous squamous cell carcinoma (SCC) that is histologically defined by loosening of the intercellular bridges resulting in acantholysis. These tumours may present as intraepidermal (in-situ) or invasive SCC.

**ICD-O code** 8075/3

**Synonyms**
Adenoid squamous cell carcinoma, pseudoglandular squamous cell carcinoma

**Epidemiology**
The acantholytic variant accounts for 2-4% of all cutaneous SCC (1149, 1687, 1819, 2549). The age range is wide but it usually affects aged individuals with a male predominance.

**Etiology**
As in conventional SCC, ultraviolet light constitutes the most important etiologic risk factor.

**Localization**
The tumour involves predominantly the skin of the head and neck region, particularly on and around the ears (1149, 1687, 1819, 2549).

**Clinical features**
ASCC presents similarly to conventional SCC, as a slowly growing scaly and occasionally ulcerated papule/plaque on the sun-exposed skin.

**Histopathology**
Invasive lesions typically show a thickened, and/or ulcerated epithelium. Scanning magnification reveals a flattened thinned, normal or hyperplastic epidermis with or without asymmetric and infiltrating dermal tumour islands. At intermediate power, prominent suprabasilar or intratumoural acantholysis is seen. Zones of acantholysis are capable of producing large intra-epidermal cavities. Acantholytic areas may extend down adjacent follicular structures involving the follicular epithelium and rarely, circumscribe the follicle simulating a glandular arrangement. Acantholytic foci may also produce a pseudovascular pattern mimicking angiosarcoma (pseudovascular SCC) (139, 1675, 1688). At high power typical features of squamous malignancy are identified including dyskeratosis, keratinocytic atypia, consisting of an increased nuclear-to-cytoplasmic ratio and nuclear hyperchromasia, altered maturation within the epithelium, and increased typical and atypical mitotic figures.

**Immunoprofile**
The lesional cells in ASCC stain for cutaneous epithelial markers that include high molecular weight keratins such as AE-2/3. Involucrin, vimentin and EMA immunostains may also be positive (1808, 2011). Low-molecular weight keratins such as AE-1, CAM 5.2 are typically negative. Various intercellular peptides have been invoked in the pathogenesis of acantholysis including the intercellular adhesion molecule syndecan, E-cadherin and the anhidrotic ectodermal dysplasia gene product (183, 1635). It has also been recently shown that decreased TP53 and PCNA expression correlated with a decrement in desmosomes seen ultrastructurally (1889).

**Differential diagnosis**
The changes described above constitute an important histologic means of separating this entity from acantholytic disorders. The differential also includes true adenosquamous cell carcinoma of the skin that exhibits squamous and glandular differentiation on ultrastructural examination and histochemical staining (2482).

**Prognosis and predictive factors**
The behaviour of ASCC like other SCCs is depth-dependent and may be more aggressive than conventional SCC (461, 1097, 1149, 1687, 1819, 1985). In-situ lesions are capable of recurrence and in up to 10% of cases, may show micro-invasion. The overall rate of metastases with lesions greater than 2.0 cm of invasion ranges from 5-19%.

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**Fig. 1.13 A** Acantholytic SCC, Intermediate-power photomicrograph depicting acantholysis extending down adjacent follicle epithelium. **B** Squamous cell carcinoma (acantholytic)
Spindle-cell squamous cell carcinoma

Definition
This is an uncommon variant of squamous cell carcinoma that exhibits a prominent spindle cell morphology.

ICD-O code 8074/3

Etiology
Lesions usually arise in sun-damaged or irradiated skin. A case has been reported in association with lichen sclerosus of the vulva (2057). The incidence of this variant may be higher in immunosuppressed patients.

Clinical features
Spindle-cell squamous cell carcinoma presents as a plaque or nodule on the skin. It may be clinically indistinguishable from the more usual type of squamous cell carcinoma. Sometimes there is a history of rapid growth.

Histopathology
It may be composed entirely of spindle cells, or have a variable component of more conventional squamous cell carcinoma. The spindle cells have a large vesicular nucleus and scanty eosinophilic cytoplasm, often with indistinct cell borders. There is variable pleomorphism, usually with many mitoses.

Differential diagnosis
It may be difficult to separate from other cutaneous spindle cell neoplasms including spindle cell melanoma, atypical fibroxanthoma and, less often, leiomyosarcoma. Some cases can only be confirmed ultrastructurally, as all keratin markers are negative (2180). CK5/6 is positive in two-thirds of all cases, a higher figure than obtained with AE1/3, CAM5.2 or MNF116. Some tumours may coexpress cytokeratin and vimentin, suggesting metaplastic change to a neoplasm with mesenchymal characteristics (1116).

Prognosis and predictive factors
Spindle-cell squamous cell carcinoma is a poorly differentiated variant of squamous cell carcinoma that may be associated with an aggressive clinical course (2180). These tumours account for slightly over one-third of cutaneous squamous cell carcinomas which metastasize (1985). Metastases usually occur to the regional lymph nodes in the first instance.

Verrucous squamous cell carcinoma

Definition
Verrucous squamous cell carcinoma is a rare variant of well-differentiated squamous cell carcinoma with low malignant potential.

ICD-O code 8051/3

Synonyms
Oral florid papillomatosis, Ackerman’s tumour (32,348), epithelioma cuniculatum (41,2096,2108), giant condyloma acuminatum, Buschke-Löwenstein tumour (359,1347,1947,2124,2570), papillomatosis cutis carcinoides (218,870, 2108).

Epidemiology
Verrucous carcinoma comprises 2-12%
Squamous cell carcinoma of all oral carcinomas, and is found predominantly in men (age peak in 5th decade, range 34-85) [348]. Verrucous carcinoma of the extremities (epithelioma cuniculatum) most often affects men in the 6th decade [2108]. The incidence of the genital type (Buschke-Löwenstein tumour) varies between 5- and 24% of all penile cancers; the tumour tends to occur in men younger than 50 years (range 18-86) [218].

**Etiology**
Leading theories of the pathogenesis include chronic irritation, inflammation and impaired immune response [2096, 2108]. Important factors for the development of oral verrucous carcinomas are poor oral hygiene with ill-fitting dentures or decaying teeth, chewing of tobacco or betel nuts, and use of snuff. In genital lesions poor hygiene and phimosis play a major role. Other theories include HPV infection (mostly HPV 6, 11) [898] and chemical carcinogens [2096,2108].

**Localization**
Common sites include buccal and retro-molar mucosa, gingiva, floor of mouth, tongue and hard palate. They also arise on the soles, rarely the palms and distal fingers, and on amputation stumps. Genital lesions occur primarily on the glans and prepuce of the penis [778, 2108,2570]. It is uncommon in the vagina and the perianal region [1347,1947, 2124]. Rare cases have been described on the scalp, face, back and extremities, sometimes associated with long-standing ulcerations or scars, especially in the pretibial area (papillomatosis cutis carcinoides) [218,870,2096,2108].

**Clinical features**
These lesions show cauliflower-like appearance with exophytic and endophytic growth, and a papillomatous surface. They are pale in colour and sometimes have draining sinuses. Some are tender and painful, particularly on the sole of the foot. There is slow but relentless growth over the course of a long time [2570].

**Histopathology**
In all cases a well-differentiated proliferative epithelial process is visible, the malignant nature of which may easily be overlooked, particularly if the biopsy is small and superficial. The squamous epithelium shows an asymmetric exo- and endophytic growth pattern with pushing rather than destructive or infiltrative margins. Usually, there is deep penetration below the level of the surrounding epidermis / mucosa. Tumour cells exhibit only minimal atypia and very low mitotic activity. The presence of neutrophils is an important diagnostic clue; they may form small intraepidermal abscesses. Draining sinuses containing inflammatory cells and keratin debris may also be present. No foci of the usual squamous cell carcinoma should be found [1833].

**Differential diagnosis**
The separation from benign reactive processes and SCC of the more usual type can be difficult. The presence of blunted projections of squamous epithelium in the mid and/or deep dermis is suspicious for verrucous carcinoma. The squamous downgrowths are bulbous. Small collections of neutrophils may extend into the tips. Clinicopathological correlation and adequate sampling are often helpful.

**Precursor lesions**
Oral lesions may develop in areas of previous leukoplakia, lichen planus, lupus erythematosus or candidiasis (218).

**Prognosis and predictive factors**
If the tumour is completely excised, prognosis is excellent; after inadequate excision, the recurrence rate is high and the survival decreases. In long-standing cases or after irradiation and / or chemotherapy the biologic character of the disease may change into a metastasizing squamous cell carcinoma [1216].

**Pseudovascular squamous cell carcinoma**

**Definition**
Pseudovascular SCC is an aggressive variant of SCC with marked acantholysis resulting in angiosarcoma-like areas [139,1688].

**ICD-O code**
8075/3

**Synonyms**
Pseudoangiosarcomatous SCC, pseudoangiomatous SCC

**Epidemiology**
The tumour is exceedingly rare.

**Clinical features**
It usually presents as a circumscribed white-grey ulcer or a nodular tan-red/pink tumour, most often located on sun-
exposed areas of middle-aged or elderly patients.

**Histopathology**
It is characterized by areas of anastomosing cord-like arrays of polygonal or flattened tumour cells, with internal pseudolumina that contain detached tumour cells and amorphous basophilic material \((550, 1675, 2558)\). Erythrocytes may also be seen in pseudovascular spaces. Immunohistochemical examination is essential to differentiate it from angiosarcoma. Pseudovascular SCC is positive for one or more monoclonal antibodies to cytokeratin and consistently negative for CD31 and factor VIII-related antigen.

**Differential diagnosis**
In classical angiosarcoma vascular markers are positive, keratin staining is negative; in epithelioid angiosarcoma in addition to vascular markers epithelial markers are frequently expressed.

**Prognosis and predictive factors**
The prognosis is worse than it is for other variants of SCC, with a mortality up to 50%. Large size may confer a worse prognosis \((1675)\).

**Adenosquamous carcinoma**

**Definition**
Adenosquamous carcinoma is a rare variant of squamous cell carcinoma arising from pluripotential cells related to acrosyringia, characterized by the formation of mucin secreting glands.

**ICD-code**
8560/3

**Epidemiology**
Most reported cases occurred on the head and neck of elderly patients, with male predominance \((120, 140, 572, 1933, 2482)\). The penis can also be involved \((120)\).

**Clinical features**
It can present as an asymptomatic smooth surfaced dermal nodule or a large ulcerated deeply invasive tumour indistinguishable from squamous cell carcinoma or basal cell carcinoma.

**Histopathology**
The tumour consists of invasive tongues, sheets, columns and strands of atypical dyskeratotic squamous cells, merging with glandular structures with epithelial mucin secretion, which can be demonstrated by a PAS, mucicarmine or alcian blue stain at pH 2.5. The mucin is hyaluronidase resistant and sialidase sensitive. Intracytoplasmic neolumina containing targetoid mucin secretions can also be seen. The tumour cells are positive for cytokeratin and epithelial membrane antigen, whereas those cells forming glands stain with carcinoembryonic antigen. There may be connection between tumour cells and acrosyringia, as well as perineural invasion.

**Differential diagnosis**
Adenosquamous carcinoma should be distinguished from mucoepidermoid carcinoma, which had been reported as adenosquamous carcinoma in early reports. Adenosquamous carcinoma has well formed glands with mucin secretion and no goblet cells. Mucoepidermoid carcinoma consists of polyglonal squamous cells and goblet cells without glands. Signet ring squamous...
Squamous cell carcinoma has foamy cytoplasmic mucin globules with displacement of the cell nucleus but no glands. Microcystic adnexal carcinoma (syringomatous carcinoma, sclerosing sweat duct carcinoma) shows a more ductal appearance with prominent tubular structures but no mucin secretion. Metastatic adenosquamous carcinoma from other primary sites such as the lung, salivary gland, female genital tract should also be excluded.

**Prognosis and predictive factors**
The tumours usually follow an aggressive course with the capacity for metastasis and local recurrence. Early superficially located tumours tend to have a better prognosis.
Bowen disease

Definition
Bowen disease (BD) is a form of squamous cell carcinoma in situ. It is a distinct clinicopathologic entity of the skin and mucocutaneous junction.

ICD-O code 8081/2

Synonyms
Squamous cell carcinoma in situ (SCCIS), intraepidermal carcinoma, bowenoid dysplasia, bowenoid squamous carcinoma in situ (BSCIS), vulvar intraepithelial neoplasia (VIN III).

The terms bowenoid dysplasia and BSCIS are customarily applied to cutaneous and mucocutaneous lesions of the male and female external genitalia. BD is no longer used in gynaecological pathology. It has been replaced by the concept of vulvar intraepithelial neoplasia (VIN). The degree of epithelial atypia seen in BD corresponds to VIN, grade III (VIN III).

Etiology
The exact underlying cause of BD remains unclear, although multiple factors are likely to be responsible for it. Many lesions arise without an apparent cause. However, it is known that chronic sun damage disrupts normal keratinocytic maturation, causes mutation of the tumour suppressor gene protein (TP53), and results in the development of keratinocytic atypia as seen in lesions of BD. The predilection for anatomic sites affected by BD on sun-exposed glabrous skin and lesions being reported more commonly in patients with a history of PUVA or UVB therapy, attest to the critical role of causal relationship between UV damage and BD. Ingestion of inorganic arsenic may play a role, as lesions of arsenical keratosis (As-K) may display identical histopathologic features to BD. A large number of cases of As-K with associated invasive carcinoma have been reported in a rural population using well water containing a high concentration of inorganic arsenic.

Epidemiology
Bowen disease occurs predominantly in fair-complexioned Caucasian men, but both sexes are affected. One in five patients (20%) is a woman. The disease commonly affects patients in the 6-8th decades of life. However, the average age at onset of the disease is 48 years, and the average age at first biopsy is 55 years. Both exposed and non-exposed skin sites are equally affected. The disease uncommonly affects black skin, in which it is found more commonly on non-sun-exposed areas.

Clinical features
The classic appearance of cutaneous BD is a single or multiple erythematous, rounded to irregular, lenticular, scaly, keratotic, fissured, crusty, nodular, eroded, pigmented patches or plaques. The plaques are devoid of hair, and usually appear sharply demarcated from the surrounding unaffected skin. Areas of normal-appearing skin may occur within the boundaries of larger lesions of BD. The plaques vary from 1-5 cm in overall dimensions. In intertriginous areas, BD may appear as moist patches without scale. In anogenital locations, the lesions appear polyoid or verrucoid, frequently pigmented. Erythroplasia of Queyrat (EPQ) presents as an asymptomatic,
bright red, velvety to shiny, sharply circumscribed plaque. The mucocutaneous junction of the glans penis, coro-
nal sulcus, or undersurface of the foreskin is involved, and lesions are usually found in older, uncircumcised men.
There are two clinical variants of BD: those involving glabrous skin, and those of the anogenital area. On the glabrous
skin, BD manifests as asymptomatic, slowly enlarging, scaly patches or plaques. The average duration of the
lesion is 6.4 years. Plaques of BD enlarge slowly, and expand centrifugally, sometimes for decades. Anogenital BD
involves the mucocutaneous junction and adjacent mucosa. If untreated, 5-8% of patients may develop invasive carci-
noma. The invasive carcinomas are larger (up to 15 cm), rapidly growing tumours that occur in pre-existing scaly plaques
{1203}.
The clinical entity of erythroplasia of Queyrat (EPQ) is regarded as BD of the glans penis. Such lesions have a greater potential for developing into invasive carci-
noma than does BD involving glabrous skin {875}. Although evidence for the association of BD and internal malignan-
cies is reported in earlier studies, more recent population-based cohort studies do not confirm the link {484}.

**Histopathology**
The typical low-power microscopic features of BD are hyperkeratosis, parakeratosis, hypo- or hypergranulosis, plaque-
like acanthosis with increased cellularity, and a chronic inflammatory infiltrate in the upper corium. The epidermis exhibits
loss of normal polarity and progression of normal surface keratinocytic maturation. A “windblown” appearance of crowding of atypical keratinocytes, with hyperchro-
matism, pale-staining to vacuolated cells, occasional multinucleated cells, individual cell keratinization (dyserkerato-
sis), and abnormal mitoses are noted. These changes are confined by an intact dermoeipidermal basement membrane.
Lesions of BD from hair-bearing areas invariably demonstrate involvement of the pilar acrotrichium, infundibulum, and
sebaceous gland. In some lesions, prominent vacuolated atypical cells focally mimic koilocytic viral cytopathic change and exhibit a pagetoid appear-
ance. The acrosyringium is occasionally involved. An inflammatory infiltrate of lymphocytes, macrophages, and plasma
cells is seen in the upper dermis. Capillary ectasia is commonly noted. Prominent solar elastosis is also present in lesions on sun-exposed skin. An invasive carcinoma arising in BD shows variable histologic differentiation, with squa-
mous, basosquamous, pilar, sebaceous {1120}, pilosebaceous, poorly-differentiated, and occasionally ductal features
{1203,2016}. The atypical vacuolated keratinocytes are negative for cytoplasmic mucin; some, however, contain
glycogen. Melanin pigment may be present in the atypical cells, and in the pigmented genital lesions, melanophages are numerous. The abnormal keratinizing cells are intensely reactive with glucose-6-phosphate dehydrogenase. Ultrastructural changes of BD include decrease in tonofilament-desmosomal attachments, aggregated tonofilaments and nuclear substance, and absence of keratohyaline granules (1204).

**Differential diagnosis**
Bowenoid solar keratosis differs from BD by its clinically smaller size, exclusive location on sun-exposed skin, and presence of superficial keratinocytic matura
tion. Bowenoid papulosis is distinguished from BD by its clinical appearance of multiple papular to coalescing lesions on the anogenital areas, and the typical microscopic salt and pepper distribution of atypical keratinocytes and mitoses in the affected cutaneous and mucocutaneous lesions, as well as frequent HPV positive koliocytotic cells (1790). The pagetoid variant of BD is sometimes difficult to distinguish from extramammary Paget disease. In the latter, mucicarmine, Cam 5.2 and CEA positive tumour cells are present in the epidermis, individually or in small nests, forming glandular structures at the dermoepidermal junction. These features are absent in BD. The vacuolated cells in BD contain glycogen and not mucin. In malignant melanoma in situ, the basal keratinocytes are replaced by neoplastic melanocytes. The presence of intercellular bridges and prominent dyskeratotic keratinocytes are features favouring the diagnosis of BD. Melanoma cells do not contain cyto
tkeratins of 54 and 66 kilodaltons (kd); the reverse applies with the cells in BD.

**Histogenesis**
It has been suggested that BD most likely originates from germinal cells of the pilar outer root sheath and the pluripotential epidermal cells of the acrotrichium. This concept is substantiated by the findings of various types of histologic differentiation in carcinoma arising in BD (1120,1203,2016). Using immunohistochemical localisation of keratin and involucrin, the atypical cells of BD exhibi
t it a diversity of differentiation (1093).

**Genetics**
The atypical keratinocytes of BD contain large numbers of aneuploid cells (241). Increased expression and mutation of TP53 observed in lesions of BD suggest that loss of normal TP53 tumour suppres
sor activity may be an important mechanism of oncogenesis in BD (375,1075, 1946). Allelic deletion of one or more 9q chromosome markers has been detected in occasional lesions of BD. However, no deletion of 9p markers was seen (1866). There have been no clonal chromosomal abnormalities by cytogenetic analysis of cell cultures from BD (1003).

**Prognosis and predictive factors**
Surgical excision with complete removal may cure BD. The origin of BD from pilar outer root sheath cells at the sebaceous gland level explains in part the high recurrence rate, following treatment with superficial curettage and desiccation, topical fluorouracil, and X-ray. Invasive adnexal carcinoma may develop in untreated plaques of BD of prolonged duration following expansile growth. The metastatic rate in these uncommon tumours was 18% and fatality was observed in 10% of cases in a large case series (1203).

**Bowenoid papulosis**

**Definition**
Bowenoid papulosis is a clinicopathological entity characterised by the presence on the genitalia of solitary or multiple verruca-like papules or plaques with histology resembling full thickness epidermal dysplasia as seen in Bowen disease.

**Synonyms**
Multicentric pigmented Bowen disease, multifocal indolent pigmented penile papules

**Epidemiology**
Bowenoid papulosis occurs mainly in young individuals and although uncommon the incidence is increasing. There is a male predominance.

**Etiology**
The etiopathogenesis of this condition almost certainly favours linkage to human papillomavirus infection particularly oncogenic types 16, 18, 33,35 and 39. DNA sequences have been identified by various workers (908,1737,2113). Consequently in females there is a higher incidence of abnormal cervical/vaginal smears both in affected patients and in partners of men with penile lesions. Whilst controversies regarding the bio-
logical potential of Bowenoid papulosis exist, with the possibility of invasive malignancy, in most cases the clinical course is benign and some lesions regress.

**Localization**
Bowenoid papulosis was first described as a condition affecting the groin (1438). It was later defined (1305,2447) as an entity involving the genitalia or perigenital areas. Isolated cases of extragenital Bowenoid papulosis have been described (902,1147).

**Clinical features**
The lesions are usually asymptomatic with variable clinical presentation: multiple generally small, round fleshy papules, isolated or confluent (2.0-20 mm), with a smooth papillomatous surface, sometimes with desquamation resembling lichenoid or psoriasiform dermatoses. The colour of lesions can vary from pink to reddish-purple to brown / black.

**Histopathology**
The histological features demonstrate epidermal atypia ranging from partial to full thickness atypia similar to in situ squamous cell carcinoma i.e. Bowen disease. On the genitalia changes may be termed vulvar intraepithelial neoplasia (VIN) III or penile intraepithelial neoplasia (PIN) III by some pathologists (570). There is loss of architecture. The basement membrane is intact. Mitoses are frequent, sometimes with abnormal forms often in metaphase. Dyskeratotic cells are also seen. Typical koilocytes are uncommon (908). The stratum corneum and granular cell layer often contain small inclusion - like bodies which are deeply basophilic, rounded and surrounded by a halo.

**Differential diagnosis**
The basophilic bodies, together with the numerous metaphase mitoses, are the features which suggest a diagnosis of Bowenoid papulosis rather than Bowen disease itself.

**Histogenesis**
A study based on histomorphology and DNA ploidy analysis has suggested that Bowenoid papulosis is a form of low-grade squamous cell carcinoma in situ (269). Electron microscopy has shown structures resembling viral particles (1274,1790) within the granular layer.

**Somatic genetics**
Many of the atypical keratinocytes of Bowenoid papulosis not unlike Bowen disease, contain large numbers of aneuploid cells. Increased expression and mutation of TP53 observed in lesions suggest that loss of normal TP53 tumour suppressor activity is likely to be an important mechanism of oncogenesis in Bowenoid papulosis. To date, there have been no clonal chromosomal abnormalities by cytogenetic analysis of cell cultures from Bowenoid papulosis.

**Prognosis and predictive factors**
Bowenoid papulosis appears in many cases to remain benign (1790) and spontaneous regression has occasionally occurred; however, close follow up is essential.
Definition
A common intraepidermal neoplasm of sun-damaged skin characterized by variable atypia of keratinocytes.

Synonyms
Solar keratosis

Epidemiology
Actinic keratoses (AK’s) usually present in older individuals. The fair-skinned, the freckled and those who do not tan easily are at increased risk. Lesions have developed in areas of vitiligo (2023, 2564). The rate is higher in men because of greater sun exposure (1049). In the Australian Caucasian population, AK’s are discovered in 40-60% of individuals over 40 (789,1515), rising to 80% in the seventh decade (1049). Patients with Rothmund-Thompson, Cockayne and Bloom syndromes and xeroderma pigmentosum are at increased risk (791).

Etiology
Both cumulative and intermittent sunlight exposure is implicated (790). Ultraviolet B (UVB) is the most harmful, but a supplemental effect of ultraviolet A (UVA) is demonstrated (694). AK’s are increased after PUVA therapy (11). UVB induces DNA thymidine dimer formation, which can target TP53, with impaired apoptosis of damaged keratinocytes in cells with two TP53 mutations (1150,1396,1696, 2602). Clonal proliferations of these cells form actinic keratoses and after further genetic damage, invasive SCC may develop. Ultraviolet light can act as an initiator and promoter of carcinogenesis (2602). Epidermodysplasia verruciformis–associated HPV types have been discovered in AK’s after renal transplantation (2354).

Localization
Sun-exposed areas are involved: face, ears, balding scalp, dorsal hands, forearms and lateral neck (2218).

Clinical features
Patients commonly present with multiple persistent, asymptomatic erythematous lesions. Most measure less than 1 cm and are hyperkeratotic. Atrophic lesions predominate on the face. Thickening and tenderness may indicate the development of invasive carcinoma.

Macrosopy
Most lesions are circumscribed <1cm scaly macules or slightly elevated papules or plaques, ranging from erythematous to grey-brown with adherent yellow-brown scale. Some are larger, more irregularly shaped and pigmented (1128), whilst others, particularly on the dorsal hands and forearms, are hyperkeratotic or verrucous (244). A keratin horn may be produced.

Histopathology
Six types of AK are described: hypertrophic, atrophic, Bowenoid, acantholytic, pigmented and lichenoid (233,1446). Most lesions reveal parakeratosis and hypogranulosis. Disordered keratinocyte maturation with cytologic atypia is present, including nuclear enlargement, hyperchromasia, pleomorphism, nuclear prominence, mitotic activity, dyskeratosis and cytoplasmic pallor. Grading as Keratinocyte Intraepidermal Neoplasia (KIN I, II and III) in a manner similar to that used for the uterine cervix (506) has
been proposed, however, invasive SCC commonly arises from KIN I or II. Lesions in which impaired maturation and atypia appear to involve the full epidermal thickness have been labelled “bowenoid actinic keratoses” (BAK) (1128). Multinucleate keratinocytes and a verrucous architecture, can be seen in AKs in the setting of immunosuppression (294,1856). The abnormal keratinization often involves the epidermis between spared acrotrichia and acrosyringia, which in contrast retain columns of normal keratinization. Some lesions show spread into the infundibular and isthmic segments of follicles or less commonly along eccrine ducts (1835). Dermal changes include solar elastosis, an infiltrate of lymphocytes and plasma cells and increased vascularity. Inflammation is most frequent in lesions of the head and neck, particularly the lips.

The hypertrophic variant shows acanthosis, papillomatosis and conspicuous hyperkeratosis with alternating parakeratosis (244). Elongation of rete ridges, dilated vessels and vertically oriented collagen bundles in the papillary dermis suggest superimposed lichenification. The atrophic AK variant is easily misdiagnosed if the basal keratinocytic atypia in a parakeratotic epidermis devoid of rete ridges is missed. Budding of the basal epidermis and extension of atypia into adnexae are common. The Bowenoid variant is difficult to differentiate from Bowen disease. Whilst some claim they are identical, others emphasize the lack of full thickness atypia, less defined edge, follicular sparing and acrosyringeal involvement in BAK (1128,2476).

The acantholytic variant reveals clefting, usually suprabasal, with varying acantholysis and dyskeratosis (1409). Keratinocyte atypia aids distinction from acantholytic dermatoses. Downward extensions of the basal epidermis can induce pseudoducts, and acantholysis may spread along appendages. The pigmented variant shows increased melanization of atypical keratinocytes and dermal macrophages (1128). The lichenoid variant has keratinocyte apoptosis and vacuolation, exocytotic lymphocytes and a band-like superficial dermal lymphocytic infiltrate including colloid bodies (2318). The epidermis in early lesions is acanthotic, but more advanced regressing lesions are atrophic with pigment incontinence. Keratinocyte atypia exceeding that expected in a reactive process differentiates this lesion from benign lichenoid keratosis. The confident identification of early SCC in an AK can be difficult (1158). Detachment of individual irregular aggre-
gates of keratinocytes from the epidermis, keratin pearl formation and extension of atypical squamous cells into the reticular dermis are helpful (1158,2476).

**Immunoprofile**
Keratin and involucrin distribution is similar to normal epidermis (1093) whilst CD95 (Fas) is lost in two thirds of AK (741) and retinoid receptors are reduced (2554). Expression of E-cadherin/catenin and TP53 increases in the progression to invasive SCC (1770,2170).

**Genetics**
There is a 2-fold risk of AK in an Australian Caucasian population carrying the glutathione-S-transferase null genotype (386), further increased by fair skin and an inability to tan. Around 50% of AK's show TP53 mutations (1696,2602) and over-expression of cyclin D1 (2235) whilst independent activation of HRAS is identified in 16% (2235,2307). The majority of TP53 mutations involve single cytosine to thymine substitution (1396,1696,2307). Progression of AK into invasive SCC may involve deletion of the 9p21 region of the p16 (CDKN2A) tumour suppressor gene (1653). Loss of heterozygosity (LOH) at four or more loci has been demonstrated in >50% of AK's in a UK Caucasian population (1350) and in just under 20% of lesions in a Japanese group (1350). PCR microsatellite analysis has exposed loss on 17p(64%), 13q(52%), 17q(46%), 9p(39%), 3p(31%) and 9q(22%) (1914). The higher rate of LOH in AK than invasive SCC could reflect the low progression rate of the former (1350). 69% of AK were aneuploid in one image analysis DNA-cytometry study (241). Recurrent chromosomal changes are numerical (+7,+20) and structural, involving the distal long arm of chromosome 4,1p31,3p13 and the centromeric region of chromosome 3 (1143).

**Prognosis and predictive factors**
Untreated AK have been reported to develop into invasive SCC in 8-20% of patients (838). AK's are also risk markers for basal cell carcinoma and melanoma (2023). Individual AK's can however be stable for many years, and may regress after sun protection. One estimate has suggested a rate of malignant transformation less than 0.1% yearly (1516, 1517). Older patients with multiple lesions followed over 10 years demonstrate a lifetime risk of progression between 6-10% (641) whilst 14% of patients with >10 AK's develop invasive SCC within 5 years (1639). Sixty percent of invasive SCC's have been proposed to develop from AK's and, more recently, contiguous AK has been identified in 82.4-97% of SCC (1085,1517,1627). Clinically hypertrophic lesions reveal invasive SCC in 36% (2290). Some classify AK as a type of SCC (791,994,1442) rather than a precursor. It cannot however be proven that AK inescapably progresses to invasive SCC. The hypothesis that AK requires further genetic aberrations before the expression of clinical malignancy, is plausible (1810).

**Arsenic keratosis**

**Definition**
Arsenical keratosis is a precancerous lesion occurring in patients exposed (therapeutic, environmental or occupational) to arsenic (2109). This is a clinicopathological diagnosis. Arsenic is concentrated in a variety of tissues, including skin, hair, and nails (49,421,2007, 2109).

**Epidemiology**
Lesions may occur after a latent period of 2 years, but usually take 20-30 years to manifest (2568). A study of 262 exposed individuals revealed characteristic keratoses of the palms and soles in over 40% (49). Other skin lesions include melanosis, Bowen disease, squamous cell and basal cell carcinoma (421,2007,2109). Visceral cancers, particularly involving the lung, and genitourinary tract can also occur (49,421,2007,2109). There is a high arsenic content in some drinking waters and naturopathic medicines (1823,2007,2109).

**Clinical features**
Arsenical keratoses begin as yellowish verrucous papules, 4-10 mm in diameter. These typically occur on thenar eminences, lateral borders of palms, base or lateral surfaces of fingers, soles, heels and toes (49). A combination of mela-
nosis and multiple keratoses in non-sun-exposed areas in adults is highly suggestive of chronic arsenic exposure (2007).

**Histopathology**
A spectrum of histological appearances exists (49,421,2007,2109). Lesions may show compact hyperkeratosis, acanthosis, papillomatosis, hypertrophic actinic keratosis-like lesions and a pattern resembling seborrheic keratosis (2007, 2109,2568). Vacuolated cells in the Malpighian layer suggest arsenical keratosis, but this is not a reliable criterion. Arsenical keratoses may spare adnexae, similar to solar-related keratoses (2109). Bowenoid arsenical keratoses may display vacuolated, dyskeratotic cells with abnormal mitoses and multinucleated giant cells (1823). Arsenical-induced pigmentation comprises melanosis and dermal arsenic deposition (49).

**Histogenesis**
The exact nature of arsenical carcinogenesis is unclear. Arsenic and its metabolites are shown to cause chromosomal abnormalities and gene amplification (421,1823,2109). Human papillomavirus may be a co-factor in the pathogenesis (820).

**PUVA keratosis**

**Definition**
PUVA keratosis is a form of keratosis that arises in response to PUVA therapy.

**Epidemiology**
There are no detailed studies on the true frequency of actinic keratoses attributable solely to PUVA, but estimates have varied from 2-5% (11,1057). There are long term epidemiological data indicating increased risk of squamous cell carcinoma in patients on high dose PUVA, recorded as 300 treatments or more (2265). More recently, phototherapy using a narrow band of ultra-violet radiation in the UVB range has been used with increasing frequency, substituting for PUVA therapy in a substantial proportion of patients (2264). There are no long-term data published as yet on the risk of actinic keratoses and squamous cell carcinoma.

**Clinical features**
PUVA keratoses resemble actinic keratoses. They occur on PUVA-treated skin.

**Histopathology**
PUVA keratoses are said to have less keratinocytic atypia than sunlight-induced actinic keratoses (2417).

high doses of UVA to epidermal keratinocytes. PUVA is used in the treatment of patients with psoriasis and other disorders. Patients treated with long-term PUVA therapy are at increased risk for development of actinic keratoses and squamous cell carcinoma.

**Fig. 1.28** Arsenical keratosis. A Arsenical keratosis with full thickness dysplasia, resembling Bowen disease. B Hyperkeratotic type.
Verrucas

Definition
Verrucas or condyloma are common, contagious, epithelial tumours caused by human papillomaviruses (HPV).

Synonyms
Verrucae vulgares (common warts); verrucae palmares (deep palmar or hand warts); verrucae plantares (deep foot warts, myrmecia); superficial plantar warts (mosaic warts); verrucae planae (plane warts, flat warts); condylomata acuminate (genital warts); condylomata plana (flat cervical condylomas, plane condylomas).

Epidemiology
HPVs are widespread in nature and the prevalence of cutaneous warts is up to 10% in children 2-12 years old, occurring with equal frequency in both sexes and regressing spontaneously in 1-2 years (1282). HPV infection of the lower genital tract is one of the most common sexually transmitted diseases among adolescents and adults. Most benign genital warts resolve spontaneously and are usually caused by HPV types 6 and 11, which are considered low-risk types as they are rarely found in high-grade genital dysplasias and almost never in invasive cancer. However, persistent infection with high-risk types, predominantly HPV-16 and 18, represents the most important risk factor for development of anogenital malignancies and their precursors, squamous intraepithelial lesions (288). HPV infection occurs by direct contact with individuals who harbour clinical or subclinical HPV-associated lesions, or indirectly via contaminated surfaces and objects. Autoinnoculation from the lesion to surrounding skin is frequently observed (1282,1641). Impaired cell-mediated immunity is associated with markedly increased incidence of viral warts, for example after organ transplantation, HIV infection, chronic lymphocytic leukaemia and lymphoma (1641).

Etiology
Verrucas are caused human papillomaviruses (HPV), a large family of DNA viruses which are epitheliotropic and induce benign and malignant epithelial tumours in skin and mucosa. The definition of an HPV type is based upon nucleotide sequence homology; more than 95 HPV types have been fully characterized to date, and additional partial DNA sequences have been obtained indicating the existence of at least 130 HPV genotypes (188,605,1738).

Table 1.01
Clinical manifestations and associated HPV types

<table>
<thead>
<tr>
<th>Skin lesions</th>
<th>Frequently detected HPV</th>
<th>Less frequently detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common, palmar, plantar, mosaic</td>
<td>1,2,4</td>
<td>26,27,29,41,57,60,63,65</td>
</tr>
<tr>
<td>Flat warts</td>
<td>3,10</td>
<td>28,29</td>
</tr>
<tr>
<td>Butcher’s warts</td>
<td>2,7</td>
<td>1,3,4,10,28</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>3,5,8,10</td>
<td>9,12,14,15,17,19-25,36-38,46,47,49,50</td>
</tr>
<tr>
<td>EV-squamous cell carcinoma</td>
<td>5,8</td>
<td>14,17,20,47</td>
</tr>
<tr>
<td>Periungual SCC</td>
<td>16</td>
<td>34,35</td>
</tr>
<tr>
<td>Other SCCs</td>
<td>EV HPV types</td>
<td>Other cutaneous types</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucosal lesions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Condyoma acuminata</td>
<td>6,11</td>
<td>42-44,54,55,70,2,27,57</td>
</tr>
<tr>
<td>High grade intraepithelial neoplasia (including cervical tumours, bowenoid papulosis)</td>
<td>16,18</td>
<td>31,33-35,39,40,51-59,61,62</td>
</tr>
<tr>
<td>Buschke-Lowenstein tumours</td>
<td>6,11</td>
<td></td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis, conjunctival papillomas</td>
<td>6,11</td>
<td></td>
</tr>
<tr>
<td>Focal epithelial hyperplasia (Heck’s disease)</td>
<td>13,32</td>
<td></td>
</tr>
</tbody>
</table>
the enzymes required for transcription or replication of viral DNA and therefore is entirely dependent on subverting cellular proteins for these functions. In particular, in HPV types 16 and 18, proteins E6 and E7 promote continued cell cycling of suprabasal epidermal cells by abrogation of the functions of TP53 and pRb respectively. HPV genomes are thereby amplified to high levels during vegetative viral replication for assembly into infectious virions after encapsulation by L1 and L2 proteins in the granular layer and above. Virus assembly does not lyse keratinocytes, but rather the infectious virus is shed with desquamating cornified cells, and viral release is facilitated by disruption of the keratinocyte intracellular filamentous network by viral E4 proteins. **Host immune response (2246,2608):** Persistent papillomavirus infections are common, indicating that HPVs have evolved mechanisms to evade immune surveillance. There is no viraemic phase, low levels of viral proteins are expressed in the basal cell layer, and extensive virus production only occurs in the more immunologically privileged terminally differentiated layers. However, a successful immune response is eventually generated in most cases, since two thirds of cutaneous warts regress spontaneously within 2 years and multifocal lesions often regress concomitantly. Cell mediated immune responses appear to be primarily responsible.

**Localization**
Warts can occur on any skin or mucosal surface. Certain HPV subtypes cause specific kinds of warts and show special affinity for particular body locations. Subtypes causing common warts are found on the hands, fingers, and palms. Periungual subtypes are often seen in nail biters. Verruca plantaris is seen on the sole of the feet. Condylomata acuminata lesions (genital HPV infection) appear on the vulva, cervix, perineum, anus, or penis. Scrotal condylomata are very rare and only seen in 1% of HIV positive males.

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**Table 1.02**
Correlation between cytopathological changes of verrucas and causal HPV types

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>HPV types</th>
<th>Epidermal changes</th>
<th>Cytopathic effect (location)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verruca vulgaris</td>
<td>2</td>
<td>Prominent</td>
<td>Eccentric nucleus; condensed heterogeneous keratohyaline granules (granular)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Prominent; endophytic</td>
<td>Large, vacuolated keratinocytes with no keratohyaline granules and small, peripherally located, ‘signet ring’ nuclei (granular)</td>
</tr>
<tr>
<td>7 (Butcher’s wart)</td>
<td>7</td>
<td>Prominent</td>
<td>Central, small, shrunken nuclei within proliferating rete ridges (granular)</td>
</tr>
<tr>
<td>Palmo-plantar</td>
<td>1 (Myrmecia)</td>
<td>Prominent, endophytic</td>
<td>Vacuolated cells with large, eosinophilic keratohyaline granules forming ring-like and sickle-like figures. Basophilic nuclear inclusions (spinous, granular)</td>
</tr>
<tr>
<td>60 (Ridged wart)</td>
<td>60</td>
<td>Acanthosis and mild papillomatosis; endophytic</td>
<td>Eosinophilic, homogeneous and solitary inclusions</td>
</tr>
<tr>
<td>65 (Pigmented plantar wart)</td>
<td>65</td>
<td>Prominent; endophytic</td>
<td>Eosinophilic, homogeneous and solitary inclusions</td>
</tr>
<tr>
<td>63</td>
<td>63</td>
<td>Prominent; endophytic</td>
<td>Intracytoplasmic, heavily stained keratohyaline material with filamentous inclusions that encase the vacuolated nucleus</td>
</tr>
<tr>
<td>Verruca Plana</td>
<td>3</td>
<td>Subtle; no parakeratosis and basket-weave like appearance of stratum corneum</td>
<td>Central, pyknotic, strongly basophilic ‘bird’s eyes’ nuclei (upper spinous and granular)</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>5</td>
<td>Nests of large, clear cells; stratum corneum loose with basket-weave like appearance</td>
<td>Basophilic cytoplasm containing keratohyaline granules of various shapes and sizes; clear nucleoplasm (upper spinous and granular)</td>
</tr>
<tr>
<td>Condyloma acuminata</td>
<td>6,11</td>
<td>Marked acanthosis, some papillomatosis and hyperkeratosis</td>
<td>Less prominent vacuolisation of granular cells</td>
</tr>
</tbody>
</table>

*a Most common associated HPV genotype

*b Epidermal changes comprise papillomatosis, compact hyperkeratosis, focal parakeratosis, hypergranulosis, acanthosis.
Clinical features and correlation with viral genotyping

Cutaneous and mucosal HPV types form two distinct groups that infect skin or mucosa, although viral tropism is not absolute (605). Clinical manifestations depend on the HPV type involved, the anatomical location and the immune status of the host (1282).

Cutaneous infections: In general, classification of warts is based on morphology and anatomic localization and cutaneous warts have traditionally been classified as verruca vulgaris or common warts, palmoplantar warts, including superficial and deep types, verruca plana or plane warts and epidermodysplasia verruciformis (EV). Recent studies suggest that histological and clinical characteristics of warts are mainly determined by viral genotype, indicating that HPV typing may allow a more accurate classification. However, the use of highly sensitive PCR techniques for HPV detection and genotyping has highlighted the presence of a greater diversity of HPV types than was previously appreciated (975). These individuals often harbour multiple HPV types, particularly epidermodysplasia-verruciformis (EV)-HPV types. These HPVs were previously thought to occur only in the context of the rare genodermatosis EV, characterised by infection with unusual, widespread, cutaneous warts and associated with increased risk of non-melanoma skin cancers harbouring EV-HPV types on ultraviolet radiation exposed sites (1492). There is also mounting evidence that EV-HPV types play a cofactor role with UVR in NMSCs arising in immunosuppressed individuals (974).

Mucosal infections: Over 25 HPV types are recognized to infect anogenital and aerodigestive mucosa (605), and subclinical infections are more common than visible warts (1282). Genital warts are generally caused by low-risk mucosal HPV types rather than the high-risk types associated with anogenital neoplasia (605). Bowenoid papulosis (section 1.5.01) may clinically resemble genital warts, but histologically resembles squamous cell carcinoma in situ and contains high-risk HPV types. Giant condyloma acuminata (Buschke-Lowenstein tumour) may also resemble genital warts but is an anogenital verrucous carcinoma harbouring low-risk HPV types (2476). Oral warts are also associated with HPV types 6 and 11 and focal epithelial hyperplasia (Heck’s disease) resembling gingival, buccal and labial flat warts or condylomata usually harbours HPV 13 or 32 (2476).

Verruca vulgaris

Definition

Verruca vulgaris is a benign, squamous papillomatous lesion caused by infection with the human papilloma virus (HPV).

Synonym

Common wart.

Epidemiology

Verruca vulgaris occurs predominantly in children and adolescents, although adults are also frequently infected. They have been found in up to 20% of school students (1262). Clinically detectable verrucae develop from a few weeks to 18 months after inoculation (1691).

Etiology

Common warts are preferentially associated with HPV-2, but they may also be caused by other types such as HPV-1, HPV-4 and HPV-7. In children, HPV-6 and/or HPV-11 are rarely found. Other HPV types have rarely been implicated, usually in immunosuppressed individuals (106).

Localization

Common warts may be solitary or multiple, and they are usually found on exposed parts, particularly the fingers and on the dorsum of the hands.

Clinical features

They are hard, rough-surfaced papules that range in diameter from about 0.2:1.5-2.0 cm. New warts may sometimes form at sites of trauma (Koebner phenomenon).

Histopathology

Common warts show marked hyperkeratosis and acanthosis. There are outgrowths of epidermis presenting as slender spires in filiform warts or blunter digitate processes in other variants. Columns of parakeratosis overlie the papillomatous projections. There may be haemorrhage into these columns. Hypergranulosis is present where the cells contain coarse clumps of keratohyaline granules. Koilocytes (large vacuolated cells with small pyknotic nuclei) are present in the upper malpighian layer and the granular layer. Small amounts of keratohyalin may be present in the cytoplasm of these cells. There is often some inward turning of the elongated rete ridges at the edges of the lesion. Tricholemmal differentiation and squamous eddies may be seen in old warts. Dilated vessels are often found in the core of the papillomatous projections. A variable lymphocytic infiltrate is sometimes seen, and this may be lichenoid in presumptive regressing lesions.

Prognosis and predictive factors

Most warts are only a cosmetic problem. Rarely, Bowen disease or squamous cell carcinoma may develop in a common wart, usually in immunocompromised patients (1611). Thrombosis of superficial vessels, haemorrhage and necrosis of the epidermis are rarely seen in regressing common warts.
Verruca plantaris

Definition
Verruca plantaris is a benign, human papillomavirus (HPV)-induced epithelial proliferation occurring on the sole of the foot. It is characterized by the formation of thick, hyperkeratotic lesions (505,648,1214).

Synonyms
Plantar wart, deep foot warts, myrmecia

Epidemiology
Plantar warts are most common in children and young adults; possibly because of immaturity of the immune system or sport-related repetitive microtrauma. They are most frequent over pressure points (505,648). Particularly in children they may spontaneously regress within a few months, but in adults and immunocompromised patients they can persist for years. Rarely chronic lesions are associated with the development of verrucous carcinoma (594).

Clinical features
Plantar warts are sharply defined, rounded lesions, with a rough keratotic surface, surrounded by a thickened horn. They tend to grow into the foot and are covered by black dots representing thrombosed capillaries (505,648,1214). They do not retain the normal fingerprint lines of the feet, as calluses (corns) do. They often occur in multiples, and can be painful (1055,2390). They are traditionally divided into the superficial warts (mosaic), which are ordinary verrucae, and deep warts (myrmecia). Several other variants have been recently described (1055,1214,1556).

Histopathology
The mosaic–type shows acanthosis, papillomatosis, hyperkeratosis, vacuolated cells (koilocytes) in the upper Malpighian layer, vertical tiers of parakeratotic cells and clumped keratohyaline granules. Myrmecia are characterized by an endophytic proliferation of rete ridges covered by thickened keratin and prominent eosinophilic intracytoplasmic inclusions. The nuclei are retained in the stratum corneum and appear as basophilic round bodies surrounded by a clear halo (505,1055,1214). Regression of palmo-plantar warts is often associated with thrombosis of superficial vessels, haemorrhage and necrosis of the epidermis and a mixed inflammatory cell infiltrate.

Pathogenesis
HPV is the established cause. Correlations between the variety of wart and the HPV type are as follows:

Fig. 1.31 Verruca plantaris. A, B Plantar wart. Note papillomatiso, acanthosis, hyperkeratosis, viral cytopathic changes.

Fig. 1.32 Verruca plantaris on the volar surface of the toe. Clinically, the lesion was painful.

Fig. 1.33 Plantar wart (myrmecia type). Nuclei are retained in the stratum corneum as basophilic round bodies surrounded by a clear halo.

Fig. 1.34 Flat wart.

Fig. 1.35 Multiple flat warts on the chin of a young female.
Keratinocytic tumours

Deep plantar wart (myrmecia) - HPV1, HPV63 (505,2390).
Common and mosaic wart - HPV2, HPV4 (1055)
Endophytic common wart - HPV4 (1055)
Ridged and flat warts (associated with or without cyst, respectively) - HPV60 (505, 1055,1214,2390)
Large plantar wart - HPV66 (1556)

Verruca plana

Definition
Verruca plana are benign, HPV-induced, slightly elevated, flat-topped, smooth papules.

Synonyms
Flat wart, verruca plana juvenilis.

Epidemiology
Verruca plana are relatively common. Children, adolescents and young adults are most frequently affected.

Etiology
HPV types 3 and 10 are most commonly associated with verruca plana. Minor trauma, atopic dermatitis and immunosuppression are possible predisposing factors (778,909,2262).

Localization
Most lesions are located on the back of the hands and fingers, distal forearm, lower leg and face.

Clinical features
Flat warts generally are smaller than common warts and typically develop as small round to oval epidermal papules measuring 1-4 mm in diameter. Lesions are mostly skin-coloured with a smooth and flat surface, but may be hyperpigmented. The number ranges from one to several hundred and the distribution is asymmetric, sometimes linear (Koebner phenomenon).

Histopathology
Histology reveals a loose hyperkeratosis with basket-weave-pattern but little or no papillomatosis as in verruca vulgaris. There is plate-like epidermal hyperplasia of about twice the thickness of the surrounding normal epidermis with compressed papillae but dilatation and tortuosity of capillaries in the papillary dermis. Superficial epidermal layers show kollodontyosis, vacuolated keratinocytes with perinuclear clearing around centrally located nuclei (so-called “birds-eye cells”) and hypergranulosis.

Fig. 1.36 Flat wart in a patient with epidermodysplasia.

Fig. 1.37 Flat wart. There are superficial vacuolated keratinocytes with perinuclear clearing.

Flat wart-like lesions can be encountered in patients with epidermodysplasia verruciformis. These lesions may show typical blue-grey cytoplasm (907,909,1491). Regression of plane warts is accompanied by superficial lymphocytic infiltrate in the dermis with exocytosis and single epidermal cell apoptosis (2476).

Prognosis and predictive factors
Flat warts commonly persist for several years. Due to immunologic rejection in some long-standing cases, lesions have disappeared almost from one day to the next showing some local inflammation without leaving a scar. There are no reports regarding recurrences in such cases. In other cases warts lose evidence of viral cytopathic change and persist as localized verrucous epidermal hyperplasia (909).
Acanthomas

Definition
Acanthomas are benign tumours of epidermal keratinocytes. The proliferating keratinocytes may show normal epidermoid keratinization or a wide range of aberrant keratinization, which includes epidermolytic hyperkeratosis (epidermolytic acanthoma), dyskeratosis with acantholysis (warty dyskeratoma) or acantholysis alone (acantholytic acanthoma). Seborrhoeic keratosis, melanocanthoma, clear cell acanthoma, large cell acanthoma and keratoacanthoma all fulfil the criteria for an acanthoma.

Epidermolytic acanthoma

Definition
A benign tumour presenting as solitary or multiple discrete lesions and demonstrating the characteristic histologic features of epidermolytic hyperkeratosis (1628, 2151).

Epidemiology
The reported age range is 3-72 years with a slight male predominance and various racial groups affected (515).

Fig. 1.38 Epidermolytic acanthoma. This lesion shows hypergranulosis and marked cytoplasmic vacuolization with clumps of eosinophilic material, sparing the basal layer.

Histopathology
Epidermolytic acanthoma is characterised by compact hyperkeratosis, perinuclear vacuolisation of the cells of the stratum Malpighii sparing only the basal layer, indistinct reticulate cell boundaries and hypergranulosis with larger basophilic keratohyaline granules than normal and intracytoplasmic amorphous eosinophilic bodies i.e. epidermolytic hyperkeratosis (14).

Genetics
Based on patterns of keratin expression determined by immunohistochemical techniques, a somatic mutation involving K1 and K10 genes has been postulated (515). Patients with disseminated disease may also have germline mutations, with offspring at risk for congenital ichthyosiform erythroderma/generalized epidermolytic hyperkeratosis.

Warty dyskeratoma

Definition
Warty dyskeratoma is a benign papulonodular lesion characterized by an endophytic proliferation of squamous epithelium typically occurring in relation to a folliculosebaceous unit and showing prominent acantholytic dyskeratosis.

Synonyms
Isolated dyskeratosis follicularis
Follicular dyskeratoma

Epidemiology
Warty dyskeratoma occurs mostly in middle aged to elderly adults (1166).

Etiology
There are no known etiological factors. A recent study showed no evidence of HPV in 13 cases using PCR (1166).

Localization
The head and neck region is most commonly involved (873, 1166, 2306, 2321). Cases arising in oral (869) and laryngeal (1185) mucosa and in a subungual (147) location have been reported. It has been suggested that lesions arising in sites devoid of hair follicles maybe a separate entity (1166).

Clinical features
Most lesions are solitary flesh coloured to
brown papules, nodules or cysts with an umbilicated or pore-like centre or central keratin plug (873,1166). Most are 1-10mm in size (873). Occasionally the lesions are multiple (121,2306).

**Histopathology**

Warty dyskeratoma is a well-demarcated endophytic lesion characterized by prominent acantholytic dyskeratosis. This results in suprabasal clefting with formation of villi which protrude into a lacuna. There is typically abundant keratin present within the centre of the proliferation forming a plug (829,873,1166,2306). Keratin pearls are commonly seen as are small cysts lined by infundibular type epithelium (1166). Mitotic figures are commonly identified and may exceed 5 per HPF (1166).

Three architectural variants have been described namely cup-shaped, cystic and nodular and combinations of these may occur (1166). There may be an epidermal collarette present and the surrounding epidermis may show papillomatosis, hypergranulosis and hyperplasia (1166). A connection to folliculo-sebaceous structures is commonly demonstrable (873,1166).

The stroma often shows a characteristic appearance with dense collagen or fibroblasts and focal intrastromal clefts. There may be an associated mixed inflammatory cell infiltrate (873,1166,2321).

**Differential diagnosis**

Comedonal Darier disease shows identical histological features and is differentiated on clinical grounds (623).

Familial dyskeratotic comedones is a rare condition which tends to spare the scalp and face and shows less marked acantholysis and dyskeratosis than warty dyskeratoma (941).

**Histogenesis**

It has been recently suggested that this lesion is a follicular adnexal neoplasm (1166).

**Acantholytic acanthoma**

**Definition**

Acantholytic acanthoma is a rare benign epidermal tumour. The lesion displays a striking characteristic microscopic feature of acantholysis that bears resemblance to that seen in several vesiculobullous disorders (320,1566,1885,2476).

**Epidemiology**

In the 31 cases reported by Brownstein (320), the patients ranged in age from 32-87 years. The median age was 60 years; the male to female ratio was 2:1.

**Etiology**

Although it is known that immunosuppression increases the incidence of cutaneous neoplasms, the role of impaired immune surveillance resulting in acantholytic acanthoma is speculative (1885).

**Localization**

Truncal skin, i.e., back, chest, or flank, is most commonly involved, followed by extremities, neck, groin, axilla, ear, scrotum and shoulder.

**Clinical features**

Acantholytic acanthoma is a solitary, keraticotic, asymptomatic to occasionally pruritic papule or nodule. Multiple lesions have been recorded in a renal transplant patient (1885).

**Macroscopy**

The scaly, flesh-coloured, hyperkeratotic growths range in size from 0.5-1.2 cm.

**Histopathology**

The tumour shows a well-defined area of papillomatous epidermal hyperplasia. There is hyperkeratosis with prominent acantholysis involving multiple levels of the epidermis. Suprabasal or subcorneal clefts with some dyskeratotic cells (corps ronds and grains) and occasional villi are noted. The upper dermis contains a variable perivascular lymphohistocytic and occasional eosinophilic infiltrate.

**Differential diagnosis**

Acantholytic acanthoma must be distinguished from other acantholytic disorders and from various acanthomas. Pemphigus, Grover disease, and Hailey-Hailey disease are disorders with more extensive clinical papulovesicular eruptions.

Epidermolytic acanthoma shows epidermolytic hyperkeratosis, and no acantholysis is present. Clear cell acanthoma contains numerous pale cells, with abundant intracytoplasmic glycogen, which is absent in acantholytic acanthoma.

**Lentigo simplex**

**Definition**

Lentigo simplex is characterized by a clinically flat epidermis with microscopic acanthosis and highly localized well-circumscribed pigment on sun exposed skin.

**Synonyms**

Solar lentigo, actinic lentigo, “ink spot” lentigo and lichen planus like keratosis.

**Epidemiology**

Lentigines are common pigmented lesions most frequently seen on the sun-exposed skin of light skinned individuals.

**Localization**

These lesions occur essentially only on skin or mucosa and spare the palms and soles. There is relative sparing of sun-protected areas, but some lesions may occur in these sites.

**Clinical features**

Lentigines are well-circumscribed mainly flat (macular) localized collections of pigment. The lesions are common and are ubiquitous in light skinned individuals. Most are somewhat randomly distributed on sun-exposed skin. The presence of many lesions may raise the consideration of a syndrome, particularly when there is extensive involvement of the lips. Peutz-Jeghers syndrome is the presence of numerous lentigines associated with multiple hamartomatous gastrointestinal polyps (893).

**Macroscopy**

Individual lesions may be smooth-edged, but many have an irregular outline. Most appear entirely uniform in colour and range from light tan to brown to black. While lesions may approach 1 cm in greatest dimension, nearly all clinical lesions are 1-5 mm.

In the large cell acanthoma variant, the tumours are macroscopically very deeply pigmented and may simulate malignant melanoma in situ.

Lichen planus like keratoses have a highly variable appearance and may show pink, orange, or rust coloured hues. Most are minimally raised from the skin surface and have a paving stone outline that is frequently polygonal rather than rounded (677).
Histopathology
All lentigines demonstrate a sharply circumscribed focus of epidermal hyperplasia. The tumours are strikingly melanized, and many retain residual melanin in the overlying stratum corneum. This pigment occasionally simulates parakeratotic nuclei seen in dermatitis, a feature referred to as “pigmented parakeratosis”.

While clinically macular, the typical lesion of lentigo simplex demonstrates a specific form of epidermal hyperplasia characterized by elongate rete ridges with somewhat club shaped or bulbous ends. This appearance is characteristic of other settings of epidermal hypermelanization, such as in melanocytic nevi. However, it is so typical of lentigines that in every circumstance where found, this form of epidermal hyperplasia is referred to as lentiginous epidermal hyperplasia.
In most circumstances where it is seen, the underlying papillary dermis demonstrates a variable amount of eosinophilic collagen deposition (or fibrosis). This may imply that the epidermal proliferation requires a scar like response in the underlying dermis. However, inflammation is an inconstant feature in these lesions (277,1634).

Because of the histologic similarity to the epidermis of melanocytic nevi, lentigines are defined partially by what is absent in the tumours: namely nevomelanocytic nests. The presence of even rare nests is sufficient to separate the diagnosis as lentiginous junctional nevus (or “jenti-go”).
Thus, to make a diagnosis of lentigo the requisite features are: localized lentiginous epidermal hyperplasia, marked epidermal hypermelanosis, and the lack of nevomelanocytic nests. In fact, despite the remarkable melanization of the tumour, increased numbers of melanocytes are not found in lentigines.

Two clinical variants are known: large cell acanthoma and lichen planus like keratosis. In large cell acanthoma, the presence of a localized proliferation of larger-than-normal keratinocytes with marked melanization is seen. These lesions are strikingly dark and are often clinically highly suspicious for malignant melanoma.
The other characteristic histologic feature of this variant is the larger than normal appearance of the keratinocytes. The reason for this feature is unknown, but may relate to the marked accumulation of melanin pigment (277,1033,1959). A final variant is the lichen planus like keratosis. While some authors maintain that a variety of lesions may develop into these lichenoid proliferations, most concur that a large proportion begin as lentigines. Several lines of evidence point to this origin and have been reviewed. Histologically, these lesions often suggest a solitary lesion of lichen planus as they were initially described. Most demonstrate hypergranulosis and a band like superficial infiltrate but unlike routine lichen planus they may show overlying parakeratosis or an inflammatory infiltrate which contains a mixture of inflammatory cell types with some neutrophils or eosinophils. Careful evaluation of most lesions demonstrates some residual lentigo simplex and pigment within dermal melanophages (1373).

Differential diagnosis
The separation between seborrhoeic keratosis and lentigo is somewhat arbitrary, but most authors describe the epidermis as flat in lentigo simplex while the skin surface is clearly raised in seborrhoeic keratosis.

Seborrhoeic keratosis

Definition
Seborrhoeic keratoses are benign hyperplastic tumours of epidermis which are more common in older individuals.

Synonyms
Seborrhoeic wart, senile wart, stucco keratosis, melanoacanthoma.

Epidemiology
Seborrhoeic keratoses are the most common of the cutaneous neoplasms and occur in the majority of elderly Caucasian patients. These lesions are by no means limited to Caucasians, but are present in numerous older individuals of any race. The lesions are unusual in children and even young adults are rarely affected. Identical histological features are seen in certain epidermal naevi.

There is no appreciable sex predilection. In part due to the very widespread incidence of the lesion, most cases are sporadic although several syndromes are associated with seborrhoeic keratosis. Recent studies support the long held belief that seborrhoeic keratosis is a clonal process in the skin (1679).
Keratinocytic tumours

Clinical features
Seborrhoeic keratoses are slightly raised, tan to brown or black papules. Sun exposed skin is especially affected, but lesions may be present on any site of the skin except for palms or soles. They often have a “stuck on” appearance and may be easily removed. Irritated lesions often demonstrate a crust and prominent hyperkeratosis which diminishes the visibility of the epidermal pigment. Thus, many of these irritated seborrhoeic keratoses are pink to red and quite scaly. Many of these lesions appear more smooth-surfaced and are mistaken for basal cell carcinoma clinically.

Many of these lesions are uniform in colour, speckled examples are common. Pigmented seborrhoeic keratoses may be mistaken clinically for malignant melanoma. There is some correlation between the many described histological variants of seborrhoeic keratosis and the clinical appearance of the tumour.

Keratoses are generally very well circumscribed clinically. Usual lesions are oval in configuration, but linear or unusually shaped lesions are common. Dermatosis papulosa nigra appears to be a form of multiple seborrhoeic keratoses of the face seen primarily in patients of African descent. This condition is not known to be associated with any type of internal malady (658).

Leser-Trélat syndrome
This syndrome is the rapid onset of multiple pruritic seborrhoeic keratoses associated with malignancy. The tumours associated have primarily been of gastrointestinal origin, but lymphomas and leukaemias have also been reported. It should be emphasized that some authors dispute the syndrome entirely and favour a coincidental association due to the high frequency of seborrhoeic keratoses in the elderly patients (955, 2110).

Histopathology
Seborrhoeic keratoses are well-defined proliferations of epidermal keratinocytes which may be endophytic, exophytic or flat. There are seven major types of seborrhoeic keratosis:

Acanthotic (common) seborrhoeic keratosis
The acanthotic type is composed of broad columns or sheets of basaloid or squamoid cells with intervening horn cysts. There may be varying degrees of hyperkeratosis, papillomatosis and acanthosis.

Reticulated seborrhoeic keratosis
This common variant is often sampled histologically because clinical examples are frequently deeply pigmented. They form a net like or retiform pattern of acanthosis.

Pigmented seborrhoeic keratosis
Pigmented seborrhoeic keratoses are in every way similar to usual seborrhoeic keratoses, but in addition demonstrate pronounced epidermal melanin pigment.

Clonal seborrhoeic keratosis
Clonal seborrhoeic keratosis is an unusual variant, which demonstrates whorled collections or nests of keratinocytes within the thickened epidermis. These foci of enlarged keratinocytes arranged in circular collections are suggestive of the epidermal collections seen in some cases of in situ squamous carcinoma, but lack the cytological atypia inherent in malignant neoplasms.

Irritated seborrhoeic keratosis
There is a heavy lichenoid inflammatory cell infiltrate in the upper dermis. Apoptotic keratinocytes are usually quite numerous. Features of the hyperkeratotic type (see below) may also be present. Sometimes there is a heavy inflammatory cell infiltrate, including neutrophils, which may not have lichenoid features. Squamous eddies are often present in the epidermis.

Hyperkeratotic seborrhoeic keratosis
This variant shows varying degrees of hyperkeratosis, papillomatosis and acanthosis. Some cases show inflammatory features similar to the irritated variant.

Flat seborrhoeic keratosis
There is mild hyperkeratosis, often mild basal pigmentation (‘dirty feet’) and only minimal acanthosis. There are no horn cysts. The cells contrast with those of the adjacent normal epidermis by being more compact.

Immunoprofile
All studies confirm the presence of keratins throughout the tumour. Some studies have also demonstrated the presence of carcinoembryonic antigen (CEA) (314,319,665).
**Differential diagnosis**

Dowling-Degos disease has lesions indistinguishable from seborrheic keratosis except for their small size and the presence of a reticulated network of adjacent lesions. The hyperkeratotic form may resemble a verruca vulgaris. Seborrheic keratoses lack parakeratotic columns overlying the digitate hyperkeratosis and there is no haemorrhage, dilated capillaries, koilocytosis or inward turning of the acanthotic downgrowths.

**Precursor lesions**

Some believe that the solar lentigo (lentigo senilis) is a precursor lesion of reticulated seborrheic keratosis. Others regard it as an early form of this lesion.

**Prognosis and predictive factors**

In a small number of cases Bowen disease coexists with seborrheic keratosis.

**Melanoacanthoma**

**Definition**

Melanoacanthoma of the skin is a benign mixed proliferation of keratinocytes and melanocytes. It is considered to be a variant of seborrheic keratosis. Melanoacanthoma of the oral mucosa is an unrelated disorder.

**Synonyms**

Melanoacanthosis, deeply pigmented seborrheic keratosis.

**Epidemiology**

Most patients are adults beyond 40 years of age. Sex predominance is not known. There are no reliable frequency data.

**Localization**

Most melanoacanthomas are located on the trunk.

**Clinical features**

Clinically, the lesion resembles a darkly pigmented seborrheic keratosis. There are no characteristic symptoms. It may resemble a melanoma with dermatoscopy.

**Histopathology**

Melanoacanthoma has the same architecture as common seborrheic keratoses. However, they stand out by their abundant dendritic melanocytes in virtually all layers of the lesion. The keratinocytes are rich in melanin granules.

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**Clear cell acanthoma**

**Definition**

Clear cell acanthoma (CCA), is a benign epidermal neoplasm characterized by the presence of glycogen-rich clear/pale cells.

**Synonyms**

Degos acanthoma, pale cell acanthoma.

**Localization**

It is usually located on the lower extremities of middle-aged or elderly individuals. Other sites are the upper extremities, head and neck, trunk, buttocks and genital area.

**Clinical features**

It usually occurs as a solitary, slowly growing, dome-shaped papule, nodule or plaque. The lesion has sharp margins, sometimes with a keratotic scale, and a red or pink colour, giving the tumour a vascular appearance. Clinical variants include multiple, pigmented, giant, atypical, cystic and polypoid CCA (345). The clinical differential diagnosis may include pyogenic granuloma, irritated seborrheic keratosis, squamous and basal cell carcinoma, melanocytic naevus and nodular amelanotic melanoma.

**Histopathology**

There is a circumscribed, sharply demarcated epidermal proliferation with psoriasiform elongation of plump and inter-connected rete ridges. The keratinocytes differ from those of the adjacent normal epidermis by their pale/clear cytoplasm containing a large amount of glycogen, best demonstrated with a periodic acid-Schiff reaction. The keratinocytes of the basal layer and the intraepidermal portion of the adnexae are not involved. Parakeratosis, infiltration of neutrophils, which may form microabscess in the stratum corneum, and the absence of the granular layer are additional characteristic findings. Dilated capillaries and a scattered inflammatory infiltrate can be observed in the papillary dermis. The presence of melanophages in the papillary dermis and an increased number of melanocytes provide clues to the diagnosis of a pigmented CCA.
**Histogenesis**
The histogenesis of CCA is not yet completely clear. Initially considered a tumour of sweat gland or hair follicle origin, these sites were later excluded because of the different cytokeratin expression compared to CCA. Some investigators hypothesized that CCA is a benign epidermal tumour of unknown etiology, probably caused by a specific disturbance of keratinocyte differentiation. The expression of involucrin and epithelial membrane antigen further suggest that CCA is derived from surface epithelium. However, since CCA shows histopathologic findings and cytokeratin expression similar to those observed in psoriasis, others believe that it might represent an inflammatory disease rather than a neoplastic process.

**Large cell acanthoma**

**Definition**
Large cell acanthoma, a benign lesion, is now considered to be a stage in the evolution of a solar lentigo to a reticulated seborrhoeic keratosis. It was thought to represent a particular type of actinic keratosis, Bowen disease, or a distinct entity. Chronic sun exposure is the probable cause of LCA.

**Epidemiology**
Most patients are middle-aged to elderly persons. Sanchez Yus et al. (1988) estimated that approximately 1-2.5 LCAs are diagnosed per 1000 skin biopsies whereas Scholl (1982) saw only 4 cases among > 1000 actinic keratoses and > 3200 seborrhoeic keratoses.

**Etiology**
Chronic sun exposure is the probable cause of LCA.

**Localization**
Most lesions tend to occur on the trunk and extremities.

**Clinical features**
The lesion resembles a solar lentigo, flat seborrhoeic keratosis or stucco keratosis. Most cases are lightly pigmented flat plaques or patches, usually less than 10 mm in diameter. Hyperkeratosis or even verrucous appearance has been described. In Black patients, LCA may present as darkly pigmented lesions. Hypopigmentation is also seen. Dermatoscopy may rule out melanoma.

**Histopathology**
Large cell acanthoma is a sharply delimited lesion standing out by its unique large keratinocytes that have about double the size both of their cytoplasm and nuclei compared to normal keratinocytes. Often, considerable numbers of melanocytes are present. Three variants have been described: a basic pattern with mild to moderate acanthosis, a verrucous pattern with papillomatosis and hyperkeratosis, and a flat-hyperkeratotic pattern. The granular layer is thick, there is usually orthohyperkeratosis and the rete ridges may be slightly bulbous. The growth fraction is low although there is a considerable proportion of both aneuploid and hyperdiploid cells.

**Differential diagnosis**
Flat seborrhoeic keratoses differ by the smaller size of the constituent cells. Solar keratoses show parakeratosis and greater nuclear pleomorphism.

**Keratoacanthoma**

**Definition**
Keratoacanthoma is a squamoproliferative tumour, mainly of hair-bearing skin. Although it has distinctive clinical and histological features, some regard it as a variant of squamous cell carcinoma.

**ICD-O code**
8071/1

**Synonym**
Well-differentiated squamous cell carcinoma (keratoacanthoma type).

**Epidemiology**
Most cases develop in older persons, particularly in the sixth and seventh decades. There is a male preponderance. Keratoacanthomas are more frequent in subtropical areas.
Etiology
Exposure to excessive sunlight is the most frequently incriminated factor in their etiology. Viruses have also been implicated, particularly in immunosuppressed patients in whom DNA sequences of HPV have been detected in 20% of cases (2270). Chemical carcinogens produce similar tumours in some animals, but their role in humans is speculative.

Localization
In temperate climates, up to 70% of lesions develop on the face. In subtropical areas, there is a much greater tendency for lesions to arise on the arms, dorsum of the hands and the lower extremities.

Clinical features
Keratoacanthomas are usually solitary, pink or flesh-coloured, dome-shaped nodules with a central keratin plug. They measure 1-2 cm in diameter. They tend to grow rapidly over 1-2 months with spontaneous involution after 3-6 months. Uncommonly, lesions persist for more than 12 months. Because local tissue destruction can occur during growth and involution, active treatment is usually advocated.

Several clinical variants occur:
- Giant keratoacanthoma, a lesion greater than 2-3 cm in diameter
- Keratoacanthoma centrifugum marginatum, which undergoes progressive peripheral growth with coincident central healing (1740)
- Subungual keratoacanthoma, a destructive form that may produce pressure erosion of the distal phalanx. They usually fail to regress spontaneously (146)
- Multiple keratoacanthomas, which may be eruptive (Grzybowski type), self-healing (the Ferguson Smith type, which is autosomal dominant in inheritance and caused by an abnormality on chromosome 9q22-q31), and a mixed eruptive and self-healing type (Witten and Zak type).
- Multiple lesions can also occur in immunosuppressed patients (625), in the Muir-Torre syndrome (see below) and at sites of trauma (1789).

Macroscopy
They are usually pale nodules with a central keratin plug.

Histopathology
Keratoacanthomas are exoendophytic, squamoproliferative nodules with a central, keratin plug. Fully developed lesions show lipping (buttressing) of the edges of the lesion which overlap the central keratin-filled crater, giving it a symmetrical appearance. Blunt downgrowths of squamous epithelium extend into the dermis with an irregular lower border to the tumour. The cells at the periphery of the squamous islands are basaloid in type. As they mature, they become large squamous cells with a distinctive pale eosinophilic cytoplasm. Mitoses may be seen, but atypical mitoses and stromal infiltration suggest a squamous cell carcinoma. SCCs are acknowledged to occur in less than 1% of keratoacanthomas found in subtropical regions. In one series, the reported incidence of a supervening squamous cell carcinoma was approximately one-quarter of all keratoacanthomas (2040).

A mixed inflammatory cell infiltrate, often including eosinophils and neutrophils may be present in the stroma. Neutrophils may extend into the epithelial nests, producing small microabscesses. Hyperplasia of sweat duct epithelium may be present in some cases. Perineural invasion is an incidental and infrequent finding, often in facial lesions. It does not usually affect the prognosis or behaviour of the lesions, although local recurrence has been reported in such cases. Several cases with intravenous...
Keratinocytic tumours
growth and a favourable outcome have been recorded (842).
Regressing keratoacanthomas are shallower lesions with a large keratin plug and buttressing at the margins. There is progressive dermal fibrosis and disappearance of tumour nests in the dermis. Foreign body giant cells may be present around residual keratin fragments. (PCNA / MIB-1 labelled proliferating cells are found in the periphery of the squamous nests in keratoacanthoma, in contrast to a more diffuse pattern in squamous cell carcinoma. Expression of TP53 is found in both tumours. Subungual keratoacanthomas have characteristic dyskeratotic cells, some showing dystrophic calcification, towards the centre of the tumour nests. This variant has fewer neutrophils and eosinophils.

The differential diagnosis from squamous cell carcinoma may be difficult or impossible in superficial shave and punch biopsies. Features favouring keratoacanthoma include the flask-like configuration with a central keratin plug, the pattern of keratinization, the large central squamous cells, the lack of anaplasia and a sharp outline between tumour nests and the stroma (555,2477).

Histogenesis
The great majority of keratoacanthomas develop on hair-bearing skin (474) and are presumed to be derived from follicular keratinocytes, perhaps with a programmed life span. Those rare tumours that arise on glabrous skin and mucous membranes presumably derive from epithelial keratinocytes.

Genetics
A genetic defect has been reported in patients with the Ferguson Smith type of “multiple self-healing epitheliomas” (keratoacanthomas). The Muir Torre syndrome, in which sebaceous tumours develop in association with visceral tumours, usually gastrointestinal cancers, and often with keratoacanthomas, epidermal cysts and colonic polyps, is inherited as an autosomal dominant trait. Mutations have been found in some cases in one of the DNA mismatch repair genes MLH1 and MSH2.

Prognosis and predictive factors
Most lesions regress spontaneously over several months (260). This regression may, in part, be immunologically mediated (1782). Even lesions with perineural and intravenous invasion have a
favourable outcome. Keratoacanthomas can recur in up to 8% of cases. This is more likely with lesions on the fingers, hands, lips and ears. Trauma may be responsible for recurrent lesions in some cases. Rare cases that have developed metastasis have been reported (1038). Possible explanations include misdiagnosis of the original lesion, the development of a supervening squamous cell carcinoma not recognized in the original material, genuine ‘rogue’ variants or transformation of the initial lesion into a squamous cell carcinoma in immunosuppressed patients (2476).

Lichen planus-like keratosis

Definition
Lichen planus-like keratosis (LPLK) is a benign lesion of the skin that represents the attempted immunologic regression of a solar lentigo, seborrheic keratosis, large cell acanthoma or other epidermal proliferative lesion (1569,2150).

Synonyms
Benign lichenoid keratosis.

Epidemiology
LPLK is a relatively common lesion. Most patients are middle-aged to elderly. There is a female predominance.

Etiology
The cause of the lesion is not exactly known. However, chronic sunlight exposure appears to be an important factor.

Localization
Most LPLKs are located on the upper trunk and upper extremities.

Clinical features
Clinically, LPLK presents as a flat, irregularly hyperkeratotic plaque with often irregular borders. It may be irregularly pigmented or pale in colour. The lesion resembles a basal cell carcinoma, Bowen disease, actinic keratosis or flat seborrheic keratosis. Itching and some pain may occur (1373). Dermatoscopy can rule out melanocytic lesions.

Histopathology
LPLK is characterized by a lichenoid lymphocytic infiltrate leading to basal vacuolar change and numerous apoptotic cells. There is hypergranulosis and hyperkeratosis, frequently with parakeratotic foci. Actinic elastosis is often present (785). Features of solar lentigo, large cell acanthoma or early seborrheic keratosis may be present at the margins. The inflammatory infiltrate often extends around the superficial vascular plexus.

Differential diagnosis
Lichenoid solar keratosis shows atypia of epidermal keratinocytes. In lichen planus, the inflammatory cells do not usually extend around the superficial vascular plexus. Furthermore parakeratosis, plasma cells and/or eosinophils may be present in LPLK. Similar changes may be seen in lichenoid drug eruptions. Clinical information may be required to separate these entities.
Melanocytic skin tumours include a large variety of benign and malignant neoplasms with distinct clinical, morphological and genetic profiles. From a clinical and public health point of view, the malignant melanomas are the most important group of skin cancers. Although less common than the familiar basal and squamous cell tumours of the skin, they are much more frequently fatal, due to their intrinsic tendency to lymphatic and haematogenic metastasis. Intermittent high-dose UV radiation is the major environmental risk factor, often in combination with endogenous factors, including genetic susceptibility. Malignant melanoma affects predominantly fair-skinned caucasians, although they also occur in ethnic groups characterized by a more pigmented skin. The sharp increase in incidence rates largely reflects lifestyle attitudes towards vacational sun exposure, but recent data indicate that this trend is now levelling off. Primary prevention and screening for early lesions are considered the most promising approach to a reduction of melanoma mortality.
## WHO histological classification of melanocytic tumours

<table>
<thead>
<tr>
<th>Malignant melanoma</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading melanoma</td>
<td>8743/3</td>
<td>Dermal melanocytic lesions</td>
</tr>
<tr>
<td>Nodular melanoma</td>
<td>8721/3</td>
<td>Mongolian spot</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>8742/2</td>
<td>Naevus of Ito and Ota</td>
</tr>
<tr>
<td>Acral-lentiginous melanoma</td>
<td>8744/3</td>
<td>Blue naevus</td>
</tr>
<tr>
<td>Desmoplastic melanoma</td>
<td>8745/3</td>
<td>Cellular blue naevus</td>
</tr>
<tr>
<td>Melanoma arising from blue naevus</td>
<td>8780/3</td>
<td>Combined naevus</td>
</tr>
<tr>
<td>Melanoma arising in a giant congenital naevus</td>
<td>8761/3</td>
<td>Melanotic macules, simple lentigo and lentiginous naevus</td>
</tr>
<tr>
<td>Melanoma of childhood</td>
<td>8720/3</td>
<td>Dysplastic naevus</td>
</tr>
<tr>
<td>Naevoid melanoma</td>
<td>8720/3</td>
<td>Site-specific naevi</td>
</tr>
<tr>
<td>Persistent melanoma</td>
<td>8720/3</td>
<td>Acral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meyerson naevus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign melanocytic tumours</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital melanocytic naevi</td>
<td></td>
<td>Persistent (recurrent) melanocytic naevus</td>
</tr>
<tr>
<td>Superficial type</td>
<td>8761/0</td>
<td>Spitz naevus</td>
</tr>
<tr>
<td>Proliferative nodules in congenital melanocytic naevi</td>
<td>8762/1</td>
<td>Pigmented spindle cell naevus (Reed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Halo naevus</td>
</tr>
</tbody>
</table>

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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O-3) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for non-invasive tumours, and /1 for borderline or uncertain behaviour.
TNM classification of malignant melanoma

**TNM classification**

1. T - Primary tumour
   The extent of the tumour is classified after excision, see pT.

2. N - Regional lymph nodes
   - N0: No regional lymph node metastasis
   - N1: Metastasis in one regional lymph node
     - N1a: only microscopic metastasis (clinically occult)
     - N1b: macroscopic metastasis (clinically apparent)
   - N2: Metastasis in two or three regional lymph nodes or intralymphatic regional metastasis
     - N2a: only microscopic nodal metastasis
     - N2b: macroscopic nodal metastasis
     - N2c: satellite or in-transit metastasis without regional nodal metastasis
   - N3: Metastasis in four or more regional lymph nodes, or matted metastatic regional lymph nodes, or satellite or in-transit metastasis with metastasis in regional lymph node(s)

   Note: Satellites are tumour nests or nodules (macro- or microscopic) within 2cm of the primary tumour. In-transit metastasis involves skin or subcutaneous tissue more than 2cm from the primary tumour but not beyond the regional lymph nodes.

3. M - Distant metastasis
   - M0: No distant metastasis
   - M1: Distant metastasis
     - M1a: Skin, subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
     - M1b: Lung
     - M1c: Other sites, or any site with elevated serum lactic dehydrogenase (LDH)

**pT - Primary tumour (pathological classification)**

- pTX: Primary tumour cannot be assessed*
- pT0: No evidence of primary tumour
- pTis: Melanoma in situ (Clark level I) (atypical melanocytic hyperplasia, severe melanocytic dysplasia, not an invasive malignant lesion)

- pT1: Tumour 1mm or less in thickness
  - pT1a: Clark level II or III, without ulceration
  - pT1b: Clark level IV or V, or with ulceration
- pT2: Tumour more than 1mm but not more than 2mm in thickness
  - pT2a: without ulceration
  - pT2b: with ulceration
- pT3: Tumour more than 2mm but not more than 4mm in thickness
  - pT3a: without ulceration
  - pT3b: with ulceration
- pT4: Tumour more than 4mm in thickness
  - pT4a: without ulceration
  - pT4b: with ulceration

Note: *pTX includes shave biopsies and regressed melanomas.

**Stage grouping**

- Stage 0: pTis N0 M0
- Stage I: pT1 N0 M0
- Stage IA: pT1a N0 M0
- Stage IB: pT1b N0 M0
- Stage IIA: pT2a N0 M0
- Stage IIB: pT2b N0 M0
- Stage IIC: pT2c N0 M0
- Stage III: Any pT N1, N2, N3 M0
- Stage IIIA: pT1a-4a N1a, 2a M0
- Stage IIIB: pT1a-4a N1b, 2b, 2c M0
- Stage IIIC: pT1b-4b N1a, 2a, 2c M0
- Stage IV: Any T Any N M1

---

3. Clinical staging includes complete excision of the primary melanoma [pT] with clinical/radiological assessment for regional and distant metastases. Pathologic staging includes complete excision of the primary melanoma [pT] and pathologic assessment of the regional lymph nodes [pN] after partial or complete lymphadenectomy. Stage 0 or stage IA patients do not require pathological evaluation of their lymph nodes.
Malignant melanoma: Introduction

Incidence and mortality

Approximately 79,000 males and 81,000 females were diagnosed with melanoma world-wide in 2002, of which about 80% occurred in the predominantly white populations of Northern America, Australia, New Zealand and Europe. On a global scale, malignant melanoma was the 16th and 15th most commonly diagnosed cancer in males and females respectively and occurred most frequently in Australia and New Zealand (4th most common males, 3rd in females), North America (6th in males, 5th in females), and Europe (16th in males, 8th in females) (724).

In 2002, around 22,000 males and 19,000 females died of the disease worldwide (724). Melanoma is one of the most important cancers when considered as a cause of loss of life as it is commonly diagnosed in relatively young people (54,310,350,1761), and can be fatal if untreated. It has been calculated that, in the United States, a person dying of melanoma would die, on average, some 17 years before the age of 65, whereas in Denmark, the mean figure is put at 14-15 years, and in Belgium 6-8 years (54,310,1761).

Melanoma had a poor prognosis in the 1950's and 1960's, but from the mid 1970s, mortality rates have been stabilising in many high-risk populations, although incidence rates are still increasing. Survival has improved substantially, mainly in countries with high incidence rates. This is mainly due to early detection of melanomas as a result of an increasing awareness of the disease, probably partly owing to the success of primary and secondary prevention campaigns.

Geographical differences

The levels of both melanoma incidence and mortality vary considerably worldwide. Rates are high in populations where Caucasians predominate, and correspondingly low in countries where inhabitants are of mainly Asian or African origin.

Melanoma in Caucasians

As the most important environmental risk factor in Caucasians is exposure to ultraviolet radiation, incidence within white populations generally increases with increasing proximity to the equator. The highest rates are observed in Australia, where many inhabitants are of Northern European descent and live in a climate with substantially more sunshine than the norm in Northern Europe.

In Western Europe, a diverging pattern is observed: incidence rates are higher in Northern Europe (more distant from the equator) than in the South, reflecting a combination of lighter skin type and higher wealth in the North of Europe. In wealthy populations, a high incidence of melanoma is observed with relatively low mortality rates, due to the fact that melanomas are diagnosed in early stages (609).

Migrant studies

Groups of migrants from regions of low melanoma incidence to high incidence regions acquire higher rates of melanoma than in their home country, but lower than those in the host country, in both sexes (96,689). Incidence and mortality rates of native Australians and New Zealanders, who are largely of British origin, are estimated to be roughly twice those of recent British immigrants to these countries (96,1255). Likewise, native Israelis experience a twofold increased risk of incidence compared to immigrants to Israel from Europe, a risk that remains at least three decades following immigration (2260). The risk of immigrants has been shown to approach that of the native populations in both Australia and Israel with increasing duration of residence in the host country (96, 533,689,1255,2260).

Amongst Northern European migrants to Australia, the incidence rates of melanoma have been observed to increase with duration of residence, but decrease with later age of arrival, suggesting that exposure at young ages is important in determining risk (1255). The lowest risk in immigrants to Australia has been found to be for Southern European and Eastern Asian migrants, reflecting the protective effect of a higher degree of skin pigmentation (1255). Differences in skin colour are also assumed to be the reason underlying the higher incidence of melanoma in white immigrants to Hawaii from the United States mainland (1031).

Melanoma in non-Caucasians

U.S. Whites have rates 15 times higher than U.S. Blacks, and a similar contrast in risk is observed in the White and Black populations of South Africa and Zimbabwe (1780). Melanoma is also relatively uncommon among Asians (1295,
Malignant melanoma: Introduction

1746) and Middle- and South-American populations (891), probably due to a better protection afforded by a larger amount of pigment in the skin and possibly different (‘wiser’) sun-exposure patterns. Melanomas appear more often on the non-pigmented areas of the skin in non-Caucasians (940), are often of the acral lentiginous melanoma type and appear on the palms of hands, soles of the feet and under the nails (200,554). A common problem in these populations is that pigmented lesions in the skin are often more difficult to notice, and are therefore often detected at relatively late stages, which, at least in part, explain the high case-fatality rates (200,554). In many African and Asian societies it is considered beautiful to have a light skin. The avoidance of sun-exposure and even more extreme measures, such as bleaching of the skin, have been reported (952,2081).

**Time trends**

Since the 1970’s there have been reports of alarming increases in melanoma, initially in terms of mortality (1393) and then in incidence (1481). These reports observed a doubling in rates every one or two decades (mean annual increments of between 3% and 7%) per annum in populations of European origin for both genders (1761). The incidence rates increased markedly for intermittently exposed body sites (trunk, legs, etc.) whereas increases in the face and neck were moderate. In males, the largest increases were found on the trunk, and in females on the legs and arms (332,459, 1007,1472,1482,1699,2120,2245,2350). In an analysis of the SEER data, it was found that melanomas of all stages increased from 1988-1997, but that localized in situ lesions increased the most (1137).

In the United States, Australia and Northern Europe, where incidence rates were very high during the 1980s, the rates have been rising less sharply or levelling off since the mid-1990’s, especially in younger age groups (516,609, 1137,1353,1472,2144,2244,2245). In contrast, in Southern and Eastern Europe and in Latin America, rates are increasing (7,609,1353,1579,2144). Incidence rates in Asia have been rather stable (1142,1295). There is insufficient data at present to report on time trends in melanoma incidence among African populations. Over the last decades, increases in incidence have mainly been observed for thin melanomas, whereas the rate of thick melanomas seems to be relatively stable (618,1433). This increase in the number of thin melanomas is mainly observed in countries with high incidence rates, where increases in rates are mainly seen in the superficial spreading melanomas (414,560,1052,1137,1472,1501). In countries with lower incidence rates, increases are generally more evenly spread across thickness categories.

Although trends in incidence rates of melanoma vary greatly, mortality rates show less variation. Mortality rates have been levelling off in many populations with high melanoma incidence rates, such as Australia, the United States, and North-western Europe (516,609,827,1353,1411,1412). In some countries, a levelling off of incidence rates is now also observed, starting in younger age groups (609).

**Stabilisation of melanoma incidence rates**

Age-period-cohort analyses indicate that in Western populations (USA, Australia, New Zealand, Sweden, the Netherlands, Germany) the increasing mortality rates have started to level off, starting in cohorts born in the 1930s and 1940s (534,827,1050,1136,1692,1983,2244,2352). In Southern Europe, generally those with lower incidence rates (e.g. Italy and Spain) there has been no sign, as yet, of a downwards trend (1480,1849,2144).

A recent plateau in melanoma mortality rates (in some cases followed by incidence rates) is reported in high-incidence countries, such as Australia, USA, Sweden, Norway and Germany (609,1353,1761,2120,2245). Only the mortal-

### Table 2.01

<table>
<thead>
<tr>
<th>Population</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blacks</td>
<td>1.00</td>
<td>0.5</td>
</tr>
<tr>
<td>Whites</td>
<td>15.4</td>
<td>11.6</td>
</tr>
</tbody>
</table>

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ty rates levelled off initially, starting in the late 1970s, with increasing incidence rates. This was most likely because of improving survival (1472, 2245,2351) due to earlier detection, as there were no major advances in systemic treatment. Melanoma incidence rates have been reported to be levelling off, or even decreasing in younger age groups, starting in the 1980s (609). Furthermore, the mean and median stage or thickness at diagnosis is decreasing (560,618,1433, 1472,2351), with an increasing registration of thin, superficial spreading melanomas. Changes in the biology of melanoma, characterized by a tendency towards less aggressive lesions being observed (353) could also be consistent with a continuing rise in melanoma incidence, and a corresponding moderation or stabilisation in the mortality rates.

**Etiology**

There has been much discussion and debate as to the reasons underlying the dramatic increases in melanoma incidence and mortality, and in particular, whether they are real or due to artefacts, via, for example, increased efforts at screening and diagnosing the disease, changes in diagnostic criteria, or the existence of a non-metastasizing biologically benign form of melanoma. Although some artefacts may have contributed to the increases, a substantial part of the increases is assumed to be genuine (610).

Both familial and environmental factors play a role in the etiology of melanoma. The familial/genetic components include skin type, number of naevi, having clinical atypical naevi, and having a family history of skin cancer. They are the most important predictors of melanoma risk. As it is not likely that there has been a substantial change over time in familial/genetic risk factors in most populations, these cannot have contributed substantially to the observed increases in melanoma incidence over the past 50 years.

**Exposure to UV radiation**

Intermittent exposure to UVR is the major environmental risk factor for melanoma, especially in combination with endogenous factors (skin types I and II, immune deficient status, genetic predisposition) (95). The association between UVR and melanoma is ambiguous, with differences in risks associated with the dose, the way it is delivered (intermittent vs. chronic exposures) and critical time periods (childhood vs. cumulative exposure during life). Intermittent exposure to UVR in white people, especially during childhood, has been postulated to be the main risk factor for the development of melanoma, although exposure in adulthood also plays a part. The relative risk of UV exposure for the development of melanoma is around 2, but when skin characteristics are taken into account, the relative risks increase markedly for those with a sun-sensitive skin. As sunbeds also emit UV-radiation, they most likely also confer a risk for the development of melanoma, as was recently confirmed in a large prospective study (2426).

Although high sun exposure in childhood is a major determinant (2509), multiple sunburns (683) and high exposure throughout life (117) raise risk of disease significantly. Cutaneous melanomas appear to arise by different pathways. Those on the head and neck relate mainly to chronic sun exposure while those on the trunk occur in people with many melanocytic naevi (2508). High numbers of naevi reflect an innate propensity to melanocytic proliferation (2196,2197) and stimulation by sun exposure (591). The risk of acral melanoma is also increased by exposure to high cumulative UVR and to agricultural chemicals (890). Occupational sun exposure, especially farming, is associated with risk of ocular melanoma (2401). Inherited mutations of tumour-suppressor genes (eg CDKN2A) are strongly associated with familial melanoma but probably underlie less than 1% of all cutaneous melanoma (42).

**Occupational vs. recreational exposure**

Before the Industrial Revolution, many wealthy people had a pale skin: they worked or stayed indoors, whereas the lower classes tended to work mainly outdoors. During the industrialisation of society (1750-1800), working class people started working indoors and only the rich had the time and money to afford recreational outdoor life. By the early 1920s, daily exposure to sunlight was also advised as a cure for many diseases (acne, rickets, tuberculosis), especially for children. By the 1930s a suntan had become a symbol for wealth and health and since the 1950s, holidays to sunny destinations became popular and affordable to many. The rising melanoma incidence is most commonly attributed to changes in lifestyle with increasing intermittent exposure to ultraviolet radiation (UVR), due to
the popularity of sunbathing and tanning. Given an induction time of some 20-40 years between exposure and melanoma occurrence, these factors are in accordance with the continuing increases - mainly on the trunk in men and on the legs in women (331,332,619,620,682,772,2409).

Ozone layer
Another explanation for the increases is the depletion of the ozone layer, which protects the earth's surface against UVR by filtering out a large part of the UVR from the sunlight before it reaches the earth's surface. Chemical substances released in the earth's atmosphere are slowly breaking down the ozone layer (2199), increasing the amount of UVR that reaches the earth's surface and likely increasing the risk of skin cancer. Estimates indicate that skin cancer incidence rates could increase dramatically by the end of this century compared to the situation around 2000 (1240).

Socio-economic status
Melanoma is more common among people with a higher socio-economic status, probably due to a higher excessive intermittent exposure to UVR (outdoor sports, winter sports, sunbathing, getting a tan) in this group. Increasing wealth over the past 6 decades in large parts of the Western (i.e. predominantly Caucasian) populations may indirectly have contributed to the increases in incidence rates of melanoma and other skin cancers.

Melanoma prevention

Sunscreens
An international group of experts convening at the International Agency for Research on Cancer investigated the preventive effects of sunscreen use on the development of skin cancer. They concluded that the use of protective cream could indeed prevent erythema and squamous cell carcinoma after non-intentional sun-exposure (i.e., exposure to the sun without the objective of getting exposed, for example, work-related exposure). Its protective effect for basal cell carcinoma and melanoma, however, is not yet determined, as it is difficult to study due to a long latency period. Paradoxically, there is inconsistent evidence that the use of sunscreens may increase the risk of melanoma development by increasing sunbathing-time. Of fifteen case-control studies examined by an expert panel, only 3 showed a significantly reduced risk of melanoma, with relative risks between 0.2 and 0.6, the others observing no significant effect (4 studies) or an increased risk (8 studies, RR between 1.7 and 3.5) (2400A). The increasing use of sunscreens may therefore have contributed to the increases in melanoma incidence.

Vaccination
Vaccination during childhood against tuberculosis with the Bacille Calmette-Guérin (BCG) vaccine or against smallpox with the vaccinia vaccine, or having experienced one or more infectious diseases may decrease the risk of developing melanomas (odds ratios between 0.29 and 0.44) (1303,1330,1331,1821,1822). Part of the increases in melanoma incidence could be due to the abolition of this type of vaccination in Europe.

Clinical features

Sites of involvement
Most commonly affected site per unit surface area of skin in both sexes is the face and male ear head and neck (772,890), with back and shoulders in men and the lower limbs in females also having high rates per unit area.

Major subtypes
Most classification schemes of melanoma categorize them clinically into four major types, but such classification has little prognostic value and diagnostic relevance, thus being of very limited usefulness in clinical practice.

Lentigo maligna melanoma.
This type of melanoma develops when an invasive tumour arises in a lentigo maligna. It is most common in the head and neck region and in elderly people, and has a relatively favourable prognosis.

Superficial spreading melanoma.
This type of melanoma grows laterally before vertical invasion develops. Increasingly, this is the most common type of melanoma in Caucasians, and has a relatively favourable prognosis being frequently observed in young patients, and on body sites that are intermittently exposed to sunlight.

Nodular melanoma
It usually presents as a rapidly growing pigmented nodule (amelanotic nodular melanomas are rarely observed), which bleeds or ulcerates. This is the most aggressive type of melanoma. It often presents on body sites that are intermittently exposed to sunlight.

Acral lentiginous melanoma
These lesions are pigmented, arising on the palm of the hand, sole of the foot or under the nails. They often present late and represent the most common type of melanoma in heavily pigmented people.

Age distribution
Malignant melanoma (hence referred to as melanoma) is a tumour affecting predominantly adults and elderly patients, with a peak of incidence around the sixth decade of life. In recent years, however, it has been increasingly recognized in middle-aged and young adults, and can be observed in children and adolescents as well. Thus, no age group is spared, and a high level of suspicion should be exerted in examination of any dubious pigmented lesion regardless of the age of the patient.

Origin
The clinical features of melanoma are variable and depend on type and stage of evolution of the tumour, and on location of it. Melanoma may occur de novo, that is, without a precursor lesion, or may develop within a pre-existing benign melanocytic naevus (1168,1750). It has been estimated that 20-30% of melanomas arise within a pre-existing melanocytic naevus, but this figure in truth may be higher, as in many instances it is very difficult to distinguish histopathologically residual complexes of a benign naevus from those of the melanoma. All types of melanocytic naevi can give rise to a melanoma, but some are more frequently involved, such as congenital melanocytic naeves. Melanoma has only rarely been observed in association with Spitz naevi (1380), but this may be due also to the difficulty in discerning histopathologically melanocytes of a melanoma from the atypical melanocytes frequently found in
Melanocytic tumours

Spitz naevi. Melanoma arising within a pre-existing blue naevus is commonly referred to as malignant blue naevus, an imprecise term that should be avoided. Melanoma may arise at the site of pre-existing scars (e.g., burn scar) (1758). Recurrence at the site of a scar from previous biopsy or narrow excision is a sign of incomplete excision of the primary tumour. Recurrence at the site of a complete excision (with negative margins verified histologically) represents locally metastatic disease rather than persistence (1000).

**ABCD rule**

The most useful criteria for clinical diagnosis of melanoma are asymmetry and uneven pigmentation of the lesion, and have been integrated in the acronym “ABCD” (Asymmetry, irregular Border, uneven Colour, Diameter > 6 mm) (1552). Although the “ABCD” mnemonic is considered the standard approach for the clinical diagnosis of melanoma, it has severe limitations when applied to early lesions of it, that may have a relatively homogenous pigmentation, sharp margins, and small diameter. Melanomas less than 5 mm in diameter have been referred to as “small melanomas” in the literature, and may be the source of diagnostic pitfalls both clinically and histopathologically (282). In addition, when assessed with the ABCD rule many benign melanocytic naevi have atypical features, thus decreasing specificity of this diagnostic criteria, too.

**Pigmentation and growth**

Most (practically all) de novo melanomas are pigmented lesions that begin as a flat macule, representing the neoplastic growth of malignant melanocytes confined to the epidermis (melanoma in situ). Lesions in this stage are characterized by a relatively homogenous brown pigmentation with slightly irregular borders. Over time (in most instances probably several years) lesions spread horizontally showing more irregular contours and variegations of the pigmentation, and revealing histopathologically involvement of the superficial (papillary) dermis. When the papillary dermis is filled by neoplastic melanocytes the lesions appear as irregular, unevenly pigmented plaques. In later stages the neoplasms exhibit vertical growth resulting in the formation of papules or nodules, usually confined to one area of the lesion. The papules and nodules represent areas where the tumour grows vertically through the dermis, eventually involving the subcutaneous tissues. In a minority of cases, melanoma exhibits a rapid nodular growth from the outset without horizontal spread, usually within a few months (so-called nodular melanoma). Finally, exceptional cases of dermal melanomas without any intraepidermal component have been recorded (2305).

**Regression**

Partial regression of part of the lesion takes place commonly during the entire process of growth of melanoma, resulting in the presence of whitish-grey areas that accentuate the asymmetry and uneven pigmentation of the lesion. In rare cases, complete regression can be observed, leading to the disappearance of all neoplastic melanocytes. Usually, these lesions show uneven pigmentation with whitish, grey and black areas corresponding to the presence of variable fibrosis and infiltrates of melanophages in the dermis. With time, the pigmentation may disappear almost completely. Although regression is an immune-mediated phenomenon corresponding to the elimination of malignant melanocytes by cytotoxic lymphocytes, complete regression of a melanoma can be associated with metastatic spread, thus being a bad rather than a good prognostic sign. The prognostic role (if any) of partial or focal regression has not yet been elucidated, but it seems negligible (764).
Melanoma is more frequent in particular settings (so-called “markers”) including a familial history of melanoma, a previous melanoma in the same patient, presence of many melanocytic naevi, presence of giant congenital naevi, skin type 1 or 2, as well as in rare conditions such as xeroderma pigmentosum among others (53,901,1196,1202,2231,2481). Patients presenting with one or more of these features should be monitored closely, and suspicious lesions should be biopsied. It is important to remember that multiple primary melanomas may be observed rarely in some patients (1196).

**Clinical variants**

**Amelanotic melanoma**

Although melanoma is a tumour characterized by variable degrees of pigmentation, in rare instances the pigment may be missing altogether (so-called amelanotic melanoma). Amelanotic melanomas are more frequent on the face, where they often display the histopathologic features of desmoplasia (desmoplastic melanoma), but can be observed also on other parts of the body (77,2285).

**Mucosal melanoma**

Melanomas arising within a mucosa (oral mucosa, genital mucosa) are often multifocal, and are characterized by dark, uneven pigmentation (670,1963). Differentiation of early lesions of mucosal melanoma from so-called melanosis (a benign condition characterized by prominent hyperpigmentation of the mucosa without or with only slight increase of melanocytes at the dermo-epidermal junction) may be very difficult or even impossible clinically as well as histopathologically.

**Subungual melanomas**

In early stages these are sometimes characterized by the presence of a well demarcated, pigmented longitudinal streak (longitudinal melanonychia) (263). The so-called Hutchinson sign (peripheral spread of the pigmentation on the proximal or lateral nail fold) may be absent in early lesions, thus representing a pitfall in the clinical diagnosis.

**Ulceration**

Rapidly growing, ulcerated melanomas may be misdiagnosed clinically as granuloma pyogenicum. Pigmentation in these cases may be scant and confined only to small areas of the tumour.

**Verrucous phenotype**

In rare cases, melanoma may present with a verrucous surface similar to what can be observed in seborrhoeic keratoses or common warts (verrucous melanoma) (101). These cases may be misinterpreted clinically as pigmented seborrhoeic keratoses or other verrucous tumours.

**Dermatoscopy**

Besides clinical examination, dermatoscopy (dermoscopy, skin surface microscopy, epiluminescence microscopy) has been increasingly regarded as a valuable aid in diagnosis of early melanoma clinically. Dermatoscopic instruments enlarge the lesion 6-100-fold, thus allowing detection of structures and signs not visible to the naked eye. In addition, connection of the dermatoscopic devices to a computer allows one to take standardized digital pictures that can be compared over time, thus being much more sensitive for detection of minimal structural changes of the examined lesion (719). Finally, computer-assisted diagnostic systems based on dermatoscopic images are available as aids for the evaluation of suspicious pigmented lesions (91).

Several dermatoscopic diagnostic approaches have been proposed, all of them relying on the examination of distinct patterns and structures. Of particular value in the diagnosis of melanoma are the presence of an irregular pigment...
network (uneven thickness of the lines, presence of broad lines at the periphery of the lesion), of black or brown dots irregularly distributed within the lesion, of irregular lines at the periphery of the lesion that are not clearly combined with the pigment network (streaks), of a blue-whitish veil corresponding to infiltrates of melanophages below a thick epidermis with hypergranulosis, of an atypical vascular pattern, and of regression structures. A 7-point checklist for dermatoscopic scoring of atypical melanocytic lesions using the aforementioned criteria has been proposed, and it has been suggested that this approach allows diagnosis of melanoma with a sensitivity of 95% and a specificity of 75% (91,1671). Other proposed approaches include the Menzies method and the ABCD rule (91). Besides dermatoscopy, the use of several other devices has been proposed for the early in vivo diagnosis of melanoma, including confocal laser microscopy (1509).

Staging
Staging investigations depend on stage and extent of the disease and should always include a complete clinical examination (2218A). Sonography of the superficial lymph nodes and of the abdomen, radiography of the thorax and evaluation of serum markers such as lactate dehydrogenase (LDH), S-100-beta or melanoma-inhibiting activity (MIA) seem to be of little value in asymptomatic patients. Computer tomography (CT) scan, magnetic resonance imaging (MRI), bone scintigraphy and positron emission tomography (PET) are useful methods for evaluation of patients with metastatic disease.

Histopathology

Architectural criteria in the epidermis

Lesional breadth
A proliferation of melanocytes wholly within the epidermis can range in size from >1 mm to a patch many cm in width. Both melanocytic naevi (conventional and Spitz) and melanoma begin as proliferations in which single melanocytes predominate.

By the time most melanomas can be recognized as such clinically they are over 4 mm in diameter, and often far broader (730). While a large lesional diameter is a finding favouring melanoma, there are many exceptions.

Symmetry of changes in the epidermis
The most important attribute of symmetry is in reference to that of melanocytes themselves. The symmetry or lack thereof in terms of the distribution of melanocytes in the epidermis is more difficult to judge than is the overall silhouette of the lesion. It is evaluated by comparing the density of melanocytes on one side of the lesion with the other; pattern of distribution of melanocytes (are they at the junction or above it) on one side of the lesion with the other; disposal as nests or as single cells on one side of the lesion with the other; cytological findings (are melanocytes on one side of the lesion different cytologically with those on the other side). Asymmetry in any of these attributes favours melanoma.

Secondary forms of asymmetry, less important that that of the distribution of melanocytes include asymmetry in pigmentation, epidermal thickness and inflammatory infiltrates. Most of these attributes are not decisive (2506).

Pigmentation in the epidermis in melanocytic neoplasms is usually in the basal layer (exceptions are particularly dark lesions, such as so-called hypermelanotic naevi) (513). In such naevi, and in very dark foci of some melanomas, there may be copious melanin in keratinocytes not only in the basal layer but also in the spinous and cornified layers. Either an asymmetrical distribution of melanoma in the basal layer of the epidermis, or melanin above the basal layer on one side of the lesion but not on the other raises the possibility of melanoma. An irregular distribution of epidermal pigment is the cause of one of the “ABCD” rules (variegated colour) of clinical diagnosis of melanoma (8). The distribution of melanophages also affects pigmentation.

Circumscription
Most melanocytic naevi have sharp borders, and melanomas indistinguishable ones. A melanocytic neoplasm is easiest to judge as well circumscribed if the edge of the lesion is defined by a nest, rather than by single melanocytes. In such cases, care must be taken that the distances between nests do not exceed or even approximate those between the most peripheral nest and the edge of the section (in other words, one must be sure that the “last” nest is truly the last one). One should also assess whether the nests at the periphery of the lesion are at irregular intervals. A lesion can have an entirely nested junctional component, with small nests at increasingly long intervals at its edges. This is often the cause of a “fuzzy” border in a dysplastic (Clark) naevus.

Predominance of single cells vs. nests
At an early stage in the intraepidermal development of a melanocytic proliferation, benign or malignant, single melanocytes in increased number will be present. Therefore, a 1 or 2 mm lesion, as noted above in which single melanocytes predominate is not necessarily aberrant. In the evolution of most acquired melanocytic naevi, the single melanocytes aggregate into nests by the time the lesion is 2 or 3 mm in diameter.

The distribution of single melanocytes is also noteworthy. One can imagine a dotted line connecting the tops of dermal papillae with one another. Very few melanocytes should reside in the epidermis above that line.

Confluence of melanocytes is another...
Confluent single melanocytes replace the basal layer in a manner such that, at least focally, keratinocytes do not seem to intervene between them. Confluence of nests of melanocytes is a more subjective determination.

**Scatter of melanocytes above the junction**

If any criterion expounded herein emblemizes intraepidermal melanoma in the minds of pathologists, it is suprabasal scatter of melanocytes. Pagetoid, buckshot and birdshot scatter also describe this distribution of neoplastic cells. It can be difficult to tell if “slight” suprabasal scatter of melanocytes is present.

Physical trauma, such as excoriation or abrasion or by ultraviolet light exposure provokes scatter of melanocytes above the epidermis (2374). Signs of physical trauma include erosion, necrosis of superficial keratinocytes, parakeratosis, subepidermal fibrin deposits and extravasation of erythrocytes in the papillary dermis. Suprabasal scatter of melanocytes is typical of naevi on acral skin (292).

**Configuration of the epidermis**

An uneven epidermal contour is more apt to be present in melanoma than in a naevus. The most typical diagnostic alteration is a thinned epidermis in the area of the melanoma (or melanoma in situ) and elongated rete ridges in an area in which a pre-existent naevus is present. In the case of melanomas in which a large mass of neoplastic cells is present in the dermis, a finding known as “consumption of the epidermis” can occur. The epidermis is thinned, and instead of small cuboidal keratinocytes in the basal layer, one sees large, flat squamous ones, often with vacuolar change. This finding is much more common in melanoma than in naevi (947).

**Kamino bodies**

The finding of many large, well formed Kamino bodies favours a Spitz naevus over melanoma. There are few convincing reports of melanomas with Kamino bodies, and these describe few, and smaller bodies. In some such reports, the bodies are not PAS-D positive, suggesting that dyskeratotic cells were mistaken for them. In addition to Spitz naevi, small

Kamino bodies occur in some dysplastic (Clark) naevi, and in some halo naevi

**Cytological features of melanoma in the epidermis**

Cytologic findings are less of a link to the correct diagnosis in the realm of melanocytic neoplasia than in other tumours. Melanocytes can be large or small, deeply pigmented or amelanotic, and vary from appearing to be round to oval to spindled to thin and dendritic. Most acquired naevi feature small round, oval or small spindled melanocytes within junctional nests. There may be no visible pigment, or some may be intracytoplasmic. In general, the amount of cytoplasm is scant in most “common” and even in most dysplastic naevi. The nuclei of such cells are usually monomorphous, allowing for different shapes due to various planes of sectioning if the cells are elongated. Melanomas with similar cytologically bland cells do occur, and the diagnosis in such cases must be made via the architectural features of the lesion.

Small melanocytes with scant cytoplasm and angulated, darkly stained nuclei are particularly apt to be found in melanomas in severely sun-damaged skin (lentigo maligna and lentigo maligna melanoma). A similar appearance can be induced by processing artefact, and by the use of some alcohol-based fixatives instead of formalin.

Large round or oval, or epithelioid melanocytes occur in both benign proliferations and in melanoma. Such cells often have abundant pale cytoplasm, with “dusty” (fine and evenly dispersed) melanin. These cells are typically seen in the intraepidermal components of melanomas of all types. Large, pale melanocytes are also present in naevi of the scalp (especially in children and teens), breast and genitalia, and in some dysplastic naevi (1532).

Spindled melanocytes occur within the epidermis in the junctional nests of dysplastic naevi and in Spitz naevi, as well as in melanoma, where their orientation is haphazard (some nests may be vertical and some horizontal). The nuclei of spindle-shaped melanoma cells are more often pleomorphic, and there is heterochromasia, i.e. some may be vesicular and some stain darkly.

Dendritic melanocytes are present in melanomas in dark skin patients in diverse settings, and light skinned ones in so-called lentigo maligna and the lentigo maligna pattern of melanoma, and in melanomas of acral-volar skin, the nail bed and of mucous membranes. The nuclei of dendritic melanocytes may be inconspicuous. The findings of dendrites that asent to the mid-spinous zone, and
especially variability in the widths of dendrites at the same level of the epidermis (anisodendrocytosis) are useful clues to melanoma in these settings. The extreme cytologic atypia typically seen in thick melanomas in the dermis and in metastases of melanoma, with very large, irregularly shaped and brightly eosinophilic nucleoli is not usually to be found in the intraepidermal component of a melanoma.

Architectural criteria in the dermis

The presence of the intraepidermal changes of melanoma is of course a clue that the dermal component of a melanocytic neoplasm might represent melanoma as well. Again, architectural criteria are more important than cytologic ones, although the balance is more even than in assessing the intraepidermal portion of a melanoma.

Symmetry

The most important aspect of symmetry of the dermal component of a melanocytic neoplasm pertains to its outline, or silhouette. Other forms of symmetry pertain to what lies within the silhouette: the composition of the neoplasm. The sizes and shapes of nests, the pigmentation and cytologic features of the melanocytes and infiltrates of lymphocytes and melanophages ideally are the same on both sides of the lesion, at the same level of the dermis. A disproportionately large nest of cells with cytologic features that contrast with those on the other side of the lesion may be a clue to melanoma.

Contour

Dysplastic naevi have a flat base at the interface between the papillary and reticular dermis, Spitz naevi have flat or wedge shaped bases, superficial blue naevi are wedge shaped, congenital and congenital-like naevi have an uneven base, with melanocytes clustered around adnexa and sometimes around vessels, and deep (often cellular) blue naevi have a lobulated base, with blunt masses of cells that protrude into the subcutis. Melanomas that involve the dermis typically have uneven, sometimes jagged bases.

Maturation

Maturation of melanocytes is in some ways a misnomer: a mature melanocyte is dendritic, and synthesizes pigment within an epithelium. The process commonly referred to as maturation is really senescence; it reflects a loss of metabolic activity, reproductive capacity and in some cases a tendency to become fat—just as mammalian senescence does. Maturation of melanocytes occurs in most naevi, with the exception of blue naevi (including deep penetrating naevi). The best-known form of maturation is the progressive diminution in the size of the nuclei of melanocytes at increasing depth within a lesion. Nucleoli also diminish in size, and if they are eosinophilic in the upper part of a lesion they tend to become basophilic at its base. Nuclear maturation in melanocytic lesions can be quantified by morphometric studies (211,1398).

In addition to nuclear maturation, the amount of cytoplasm is less at the base of a benign melanocytic neoplasm than in its upper nests. If the cytoplasm of the upper cells of a naevus is pigmented, its lower cells tend to be less pigmented or achromic. The sizes of aggregations of melanocytes also should be smaller toward the bottom of a benign neoplasm of melanocytes. The scientific basis of maturation rests on changes in metabolism (less tyrosinase activity and more acetylcholinesterase activity) and telomeric exhaustion (865,1620). Maturation occurs to a limited extent in some melanomas, but in most there are cells at the base of the lesion nearly as large as those at the top, and dispersion from large nests to small ones and single cells is often absent (1989). Pigmentation near the base of a melanocytic neoplasm can also be a clue to melanoma, but it commonly occurs in blue naevus.

Mitotic activity

Mitoses in the dermal portion of a lesion do not mandate a diagnosis of melanoma. As a rule, the mitotic figures in benign naevi are found in melanocytes within the papillary or superficial reticular dermis. If the lesion in question only extends to this depth, the number of mitoses becomes important, as does the question of whether the mitoses are in clusters (reflecting “hot spots”) or are atypical. Atypical (asymmetric, tripolar or ring) mitotic figures can occur in Spitz naevi, but are rare in other forms of naevus. Ki67 / MIB-1 marks cells that are actively cycling, and the number of such
cells should diminish toward the bottom of a benign melanocytic neoplasm. The finding of a low proliferation rate is no guarantee of benignancy. A high rate in a lesion thought to be benign should trigger reassessment.

**Cytologic features of melanoma in the dermis**

The cells of a melanoma may be large or small melanocytes, round or spindled, amelanotic or deeply pigmented. Large spindled melanocytes comprise the dermal component in some melanomas. They often are not reliably demarcated from each other by clefts, as is the case in Spitz naevi. They can form elongated, sometimes sinuous fascicles, especially in melanomas with neuroid differentiation and in desmoplastic melanomas. The spindled melanocytes of desmoplastic melanoma can also be found singly between thickened collagen bundles. They tend to be hyperchromatic, and have irregular nuclear membranes and small nucleoli. Melanocytes with abundant pale cytoplasm and dusty melanin (large, pale melanocytes) are typically present in the dermis in some dysplastic naevi, naevi at special sites (scalp, breast and genitalia) and in deep penetrating naevi. They are a common cytologic type in melanoma, especially in the superficial spreading and nodular patterns.

Small round melanocytes with scant cytoplasm, resembling those of the mature portion of a naevus can predominate in naevoid melanomas

**Radial and vertical growth**

**Radial growth phase**

Most melanomas evolve through an initial stage of tumor progression, as a flat or plaque-like lesion which expands along the radii of an imperfect circle. Because of this clinical analogy, this phase has been termed the “radial growth phase” (494). The radial growth phase may be in situ (confined to the epidermis), or in situ and invasive, but in the latter case the cells do not have capacity for proliferation in the dermis (674,832). Proliferation in the epidermis may give rise to a pattern of single cells, or of clusters or nests of atypical neoplastic melanocytes. Like the cells of junctional nevi, which may migrate into the dermis to form compound nevi, the cells of in situ melanomas may migrate into the papillary dermis. In the dermis, these cells may either undergo apoptosis and disappear (1070), or may survive without proliferating. In the latter case, the lesional cells may persist in the dermis, but they do not expand to form a tumorigenic nodule.

**Vertical growth phase (tumorigenic)**

In the next phase of progression, a tumor nodule appears either within the confines of a pre-existing plaque, or, sometimes, de novo in a lesion which is then termed “nodular melanoma” (675) cells. The key biological feature of vertical growth phase is the ability of the lesional cells to survive and proliferate in the dermis. This ability may be manifested by growth to form a true “tumour” or swelling, or by the presence of mitotic activity. Tumorigenic vertical growth is easily recognized when there is a bulky nodule present. In thin lesions, such as AJCC stage I melanomas, either of two criteria suffices for the diagnosis of vertical growth phase, namely the presence of either “tumorigenicity” or “mitogenicity”. The term “mitogenic” refers to the presence of any mitotic figures in lesional cells in the dermis. The term “tumorigenic” is here defined as the presence of a cluster of cells in the dermis larger than the largest intraepidermal cluster.

**Metastatic spread**

Most distant metastases from melanoma become evident clinically or are detected during follow-up visits within a few years from excision of the primary tumour. However, it is important to remember that late metastases (>10 years, sometimes even over 25 years after excision of the primary tumour) are not uncommon in this neoplasm (566,2088). The reason why “dormant” metastases begin to grow after such a long time is yet unknown. In most patients with metastatic disease, the regional lymph nodes are affected first, but distant metastases may be observed in patients who do not have obvious lymph node involvement. Besides lymph nodes, the most common site of metastatic spread is the skin. Visceral metastases are more frequently located in the lungs, liver, central nervous system, and bones, but any organ may be affected.

In 1992, sentinel node (SN) biopsy was proposed as a minimally invasive procedure that provided accurate assessment of regional node status in melanoma patients (1655), allowing full regional node dissection to be avoided in the 80% of patients who had negative SNs. The SN concept is simple: lymph draining from a tumour site passes first to a so-called sentinel node before onward

| Table 2.02 Melanoma antigens
<table>
<thead>
<tr>
<th><strong>Type of antigen</strong></th>
<th>Antigen</th>
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<tbody>
<tr>
<td><strong>Differentiation antigens</strong></td>
<td>Tyrosinase, gp100, Melan-A/MART-1, TRP-1, TRP-2, M C1R, AIM-1</td>
</tr>
<tr>
<td><strong>Gangliosides</strong></td>
<td>GM 1, GD 1, GD 2, GM 2, 0-acteyl GD 3</td>
</tr>
<tr>
<td><strong>Mutated proteins</strong></td>
<td>CDK4, B-catenin, CDC27, MUM-2, triosephosphate isomerase</td>
</tr>
<tr>
<td><strong>Products of unusual DNA transcripts</strong></td>
<td>TRP-2, N-acetylglucosaminyl transferase</td>
</tr>
<tr>
<td><strong>Cancer / testis antigens (CTAs)</strong></td>
<td>MAGE, BAGE, GAGE, RAGE, NY-ESO-1</td>
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passage to other nodes in the regional node field. Thus the SN is most likely to contain tumour cells, and if none are present in this node, tumour cells are unlikely to be present in other nodes in the node field. Within 3 years of the landmark publication by Morton et al (1915), confirmation of the accuracy of such assessment was provided by studies in the USA (1915) and Australia (2347).

It soon became clear that identification of this node was most accurate if three methods were used: a preoperative lymphoscintigram, injection of blue dye around the primary melanoma site immediately preoperatively, and the use of a hand-held gamma probe intraoperatively. Preoperative lymphoscintigraphy for many melanoma patients before SN biopsy provided important new insights into cutaneous lymphatic drainage pathways (2348,2396) and this new information highlighted the importance of preoperative lymphoscintigraphy before undertaking a SN biopsy procedure. The prognostic value of determining SN status has now been shown in several large studies. All show a large difference in probability of 5-year survival between patients who are SN positive and those who are SN negative, independently of other prognostic variables. Results from the Sydney Melanoma Unit (2565) are typical, with a 5-year survival rate of 56% for SN positive patients (n=145) and 90% for SN negative patients (n=846). Prognostic information from SN biopsies may be further refined by PCR to detect melanoma-specific mRNA in lymph nodes that are negative by standard histopathological techniques (1916). SN assessment not only provides important prognostic information; recent clinical trials suggest that as an removal, with complet regional node field dissecion if micrometastatic melanoma is found, improves the survival of patients (1655A).

**Stage distribution**

Survival from melanoma is related to stage at diagnosis. The stage distribution is generally more favourable in high-resource settings, and thus countries with high incidence rates tend to also have better survival than lower incidence (and lower resource) countries (608, 1472,2245;2351).

Most melanomas are localized in high incidence countries and the proportion that are localized continues to increase with time. Of the cases reported in the U.S. SEER program 1992-1998, 82% had localized disease, 9% regional disease, 4% distant metastases, and 6% were unstaged (186).

Young patients and women are often diagnosed with melanomas that have a thinner Breslow thickness than older patients and men. Because of the shift in the stage distribution of melanomas towards thinner lesions, together with a disproportionate increase in incidence relative to mortality, some have questioned whether some of these thin lesions that were removed would have ever progressed to metastatic disease (353).
Differentiation markers
These markers indicate melanocytic differentiation which is manifested by signs of melanin synthesis. Hereby cells of the melanocytic lineage are identified, but also ectopic melanin synthesis in cells of other lineages. Differentiation markers show a broad expression in many benign melanocytic lesions and (most) primary melanomas. However, in melanoma metastases expression decreases which is accompanied by heterogeneity.

Progression markers
These markers are preferentially expressed in one or few stages in melanocytic tumour progression. Based on their tissue distribution, early, intermediate and late progression markers are discerned. Progression markers include molecules that are involved in key processes in the pathogenesis of metastasis, i.e. proliferation, migration and matrix degradation. They may be derived from the neoplastic cells and/or the stromal cells, and serve as targets for various clinical interventions.

Other markers
These represent molecules that cannot be incorporated into either of the above groups.

Clinical applications
The markers mentioned can be used for several clinical applications (392). For this purpose currently immunohistochemistry on paraplast embedded tissue sections is applied, preferentially employing a red chromagen in order to contrast with the brown colour of melanin. For some applications RT-PCR is used.

Differential diagnosis of poorly differentiated malignant tumours
In case of a differential diagnosis between poorly differentiated carcinoma, sarcoma, lymphoma and melanoma a panel of various differentiation markers is applied. Melanoma is likely if the tumour is diffusely staining for S-100 and the markers for the other diagnostic options are negative. Given the low specificity of S-100 for melanocytic differentiation the diagnosis has to be substantiated. For this purpose MART-1 (syn. Melan-A) is a powerful marker both having a high sensitivity and specificity. Its sensitivity is higher than gp100 (recognized by HMB45) in cutaneous melanoma and metastasis, although in non-cutaneous melanoma it may be the reverse.

Immunotherapy
Vaccination trials have been started using gp100 and tyrosinase presented by dendritic cells, and MAGE3. Patients are selected on the basis of an appropriate HLA haplotype and extent of antigen expressed (611). Expression of gp100 and tyrosinase is estimated on immunohistochemically stained melanoma slides; for MAGE3 RT-PCR is used.

Genetic susceptibility
If melanoma runs in the family (i.e. if a parent or sibling was diagnosed with a malignant cutaneous melanoma), the relative risk of developing a melanoma compared to persons without a family history of melanoma is 2-3 (1006) and some melanoma pedigrees have been discovered. Clustering of melanoma in families is however not frequent and the genes implicated in large melanoma families probably only play a small role in population-based melanomas. Two genes have been discovered in melanoma families: CDKN2A (p16) on chromosome 9p21, and CDK4 on chromosome 12. Mutations in the CDKN2A gene have been found in up to 25% of melanoma families worldwide, whereas CDK4 has only been observed in a few rare families. The CDKN2A/p16 gene acts as a tumour suppressor gene and plays a crucial role in cell cycle regulation and senescence. The p16 protein is a cyclin-dependent kinase inhibitor which works by binding to CDK4. The p16 gene tends to be transmitted in an autosomal dominant fashion. Its penetrance varies with population incidence rates, indicating that the same factors that affect population incidence of melanoma may also mediate CDKN2A penetrance. The frequency of mutated p16 in the general population is estimated to be 0.01% (176).

Table 2.04
Prognostic indicators for melanoma.

<table>
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<tr>
<td>Histology</td>
<td>Superficial spreading melanoma</td>
</tr>
<tr>
<td>Age</td>
<td>Young</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
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<tr>
<td>Body site</td>
<td>Not on the trunk, hands, feet</td>
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<tr>
<td>Ulceration</td>
<td>Absent</td>
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<td>Mitotic index</td>
<td>Low</td>
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Melanoma antigens
The term “melanoma antigen” is used two-fold. Firstly, it refers to a large variety of molecules recognized by (monoclonal) antibodies, that were generated to explore their potential as biological and/or clinical markers. Secondly, melanoma antigen in a strict sense implies a tumour molecule that evokes an immune response in the autologous host (1944). Some overlap exists between genuine melanoma antigens and melanoma markers. Melanoma antigens currently are used in vaccination trials.

Melanoma markers
Three groups of markers can be distinguished:

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If melanoma runs in the family (i.e. if a parent or sibling was diagnosed with a malignant cutaneous melanoma), the relative risk of developing a melanoma compared to persons without a family history of melanoma is 2-3 (1006) and some melanoma pedigrees have been discovered. Clustering of melanoma in families is however not frequent and the genes implicated in large melanoma families probably only play a small role in population-based melanomas. Two genes have been discovered in melanoma families: CDKN2A (p16) on chromosome 9p21, and CDK4 on chromosome 12. Mutations in the CDKN2A gene have been found in up to 25% of melanoma families worldwide, whereas CDK4 has only been observed in a few rare families. The CDKN2A/p16 gene acts as a tumour suppressor gene and plays a crucial role in cell cycle regulation and senescence. The p16 protein is a cyclin-dependent kinase inhibitor which works by binding to CDK4. The p16 gene tends to be transmitted in an autosomal dominant fashion. Its penetrance varies with population incidence rates, indicating that the same factors that affect population incidence of melanoma may also mediate CDKN2A penetrance. The frequency of mutated p16 in the general population is estimated to be 0.01% (176).
Other genes, such as MC1R (Melanocortin 1 Receptor) and DNA repair genes, are likely to be more important in determining susceptibility for melanoma in the general population. The MC1R gene is involved in skin and hair pigmentation and in senescence and immunity (176,251,2385). Patients with inherited abnormalities in the DNA repair system, like xeroderma pigmentosum patients, are at a 1000-fold increased risk (891).

Prognosis and predictive factors

Melanoma thickness, body site, histological type of the melanoma, gender of the patient and ulceration are important indicators of patient prognosis (130). Generally, older patients do less well than younger patients for the same tumour thickness, while females do better than males. Superficial spreading melanomas generally have a better prognosis compared with other histological subtypes, because they usually have a thin Breslow thickness (1471). One report suggests that sun exposure is associated with increased survival from melanoma (224).

Reports on prognosis from specialized centres (130), may contain survival rates lower than reported by population based cancer registries (2051), possibly because patients with less favourable prognosis are being referred to specialized centres.

Morphological prognostic factors

Several clinical and histologic attributes are useful in predicting the probability of survival for patients with melanoma, and, as targeted therapies begin to be developed, no doubt these or similar attributes may be useful in predicting therapeutic responsiveness. Staging of melanoma has been discussed above, and in the 2002 AJCC classification, this staging includes clinical as well as histologic attributes (130). The basic purpose of staging is to describe the clinical extent of disease. This may be done by physical exam, by clinical investigations, and by gross and microscopic pathologic examination. The process of predicting prognosis using pathological attributes may be referred to as “microstaging”. Some of these attributes useful in prognostication are discussed below.

Clark’s levels of invasion

First described in 1967, these attributes along with Breslow’s thickness measurements are the best known prognostic attributes for melanoma (492). In Clark’s level I, the melanoma is confined to the epidermis (melanoma in situ). In level II, melanoma cells are present in the papillary dermis, which may be expanded but has not filled by tumour. Most level II melanomas are non-tumourigenic, but a few meet criteria for tumourigenicity discussed above. In level III, there is a tumour that fills and expands the papillary dermis. In level IV, tumour cells infiltrate to the collagen fibres of the reticular dermis which unlike the papillary dermis are not specialized maintain epithelium. In level V, the subcutaneous tissue is infiltrated.

Breslow’s thickness

According to Breslow’s definition, published in 1969, thickness is measured from the top of the granular layer to the deepest invasive tumour cell. This can occasionally be misleading, for example when there is marked epithelial hyperplasia but only a few tumour cells are present in the dermis. In the 2002 AJCC staging system, thickness is grouped in 1 mm intervals (130). If only one attribute is known, thickness is the single strongest prognostic attribute for melanoma.

Ulceration

Ulceration is a significant stage modifying factor in the 2002 AJCC classification. For any given thickness level, the prognosis is significantly worse when ulceration is present. In “thin” melanomas (Breslow thickness less than 1 mm) this remains true however only a few melanomas are ulcerated. Ulceration loses its significance when mitotic rate is included in a population based multivariable prognostic model (160).

Mitotic rate

Mitotic rate was the single strongest attribute in the 1989 Clark prognostic model, which was developed in a cohort of patients all of whom had vertical growth phase. Patients with a mitotic rate of six or greater were at approximate twelve-fold greater risk of metastasis than patients whose tumours had no mitoses (491). In addition, the presence of any mitoses at all in the dermis (“mitogenicity”) is predictive not only of survival (831) but also of sentinel lymph node positivity (1251).

Tumour infiltrating lymphocytes

First demonstrated in the 1989 Clark model (491) and later confirmed by others (502,1609), the presence of “brisk” tumour infiltrating lymphocytes (lymphocytes present among and in contiguity with tumour cells) is almost as powerful an attribute as mitotic rate.

Lymphovascular invasion

Although not commonly observed, and therefore not found to be an independent factor in most prognostic models, vascu-
lar invasion when present appears to be associated with a worse prognosis \((1213)\).

**Radial growth phase regression**

Several studies have demonstrated worse prognosis when radial growth phase regression is present \((491)\). Possibly in these cases, a small area of tumourigenic vertical growth phase was present before the regression obliterated it.

**Microscopic satellites**

Like clinical satellites, microscopic satellites are indicative of a lesion with competence for metastasis and are associated with a worse prognosis \((962)\).

**Patient gender and lesional cell location**

In most series, even when other prognostic factors are controlled, female patients have better survivals, and the survival is better for patients whose lesions are on the limbs compared to the trunk or extremities \((491)\).

**Immunoprofiling for the assessment of prognosis**

Two strategies are followed:

1. Identification of markers suggestive of aggressive subpopulations in primary melanoma \((1990)\). For this purpose late progression markers are used. Only a limited number of progression markers have prognostic implication independent of the conventional dominant factors, i.e. tumour thickness and ulceration. A list of prognostic markers is presented in Table 2.5. It should be noted here that the clinical relevance of these markers is increasing as the primary melanomas currently diagnosed are relatively thin \((1.0-1.5 \text{ mm})\) and rarely show ulceration. It is expected that a set of prognostic markers may help to select melanoma patients for adjuvant therapy. Such a set may be designed on the basis of the outcome of ongoing expression array studies.

2. Microstaging. The presence of melanoma deposits in various stages of the disease is assessed by the demonstration of differentiation markers. However, they may decrease during tumour progression and do not reveal the aggressiveness of the tumour cells. Nevertheless, the extension of the primary tumour that includes thickness measurement and identification of microsatellites, can be facilitated by S-100 or MART-1 immunohistochemistry. This also is applicable for the detection of melanoma cells in sentinel nodes. Immunohistochemistry on serial sections is preferred to molecular staging of sentinel nodes as it has a similar sensitivity, a higher specificity and it preserves morphology.

### Table 2.05

Prognostic markers in malignant melanoma

<table>
<thead>
<tr>
<th>Marker</th>
<th>Expression</th>
<th>Prognosis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67</td>
<td>↑</td>
<td>−</td>
</tr>
<tr>
<td>PCNA</td>
<td>↑</td>
<td>−</td>
</tr>
<tr>
<td>Cyclin A</td>
<td>↑</td>
<td>−</td>
</tr>
<tr>
<td>p16</td>
<td>↓</td>
<td>−</td>
</tr>
<tr>
<td>αvβ3</td>
<td>↑</td>
<td>−</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>CD44</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>MMP-2</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>t-PA</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>gp100</td>
<td>↓</td>
<td>−</td>
</tr>
<tr>
<td>Mitf</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>c-kit</td>
<td>↓</td>
<td>−</td>
</tr>
<tr>
<td>c-myc</td>
<td>↑</td>
<td>−</td>
</tr>
<tr>
<td>p53</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>Osteonectin</td>
<td>↑</td>
<td>−</td>
</tr>
</tbody>
</table>

¹: Unfavourable: +: favourable
Superficial spreading melanoma

Definition
Superficial spreading melanoma (SSM) is a subtype of melanoma which tends to occur on usually covered skin and is characterized by a radial growth phase comprised of large neoplastic melanocytes that extend among keratinocytes in a “buckshot” or pagetoid pattern \( (493, 494) \). It is controversial whether SSM is truly different from other melanoma forms of the skin or whether the differences are only due to differences in the skin architecture \( (22) \).

ICD-O 8743/3

Synonym
Pagetoid melanoma.

Epidemiology
SSM makes up almost two thirds of all melanomas in light-skinned people (Fitzpatrick skin types 1–3) and is thus the most frequent subtype of all melanomas. The sex incidence is identical in most areas.

Etiology
Its etiology is not exactly clarified, however, repeated severe sunburns in childhood appear to play an important role. Intermittent sun exposure in adult life is also important.

Localization
SSM may appear on almost the entire body, particularly on sites with acute-intermittent sun exposure. SSM in women is most frequently observed on the legs, in men more commonly on the trunk.

Clinical features
Signs and symptoms
SSM in situ begins as an irregularly pigmented and outlined macule. With the onset of invasion, it develops into a slightly raised plaque. Its borders are usually sharply delimited, often irregular indicating progressive peripheral extension, but they may also be ill-defined. The pigmentation within an individual lesion varies from light to dark brown to even jet-black. Grey or white areas indicate regression. White vitiliginous areas, sometimes even poliosis (white hair) may be observed. Red areas are due to inflammation or increased vascularity. Some SSMs are amelanotic, resembling Bowen or Paget disease. The tumour may reach a considerable diameter until it develops a papule representing the transition from the radial growth to vertical growth phase of SSM. These papules tend to become erosive, ulcerated and crusted with a tendency to easy bleeding. In rare instances satellite nodules are present. Most lesions are asymptomatic, but can present with bleeding once the lesion ulcerates.

Histopathology
SSM in situ or the intraepidermal part of an invasive lesion stands out by pagetoid spread throughout the epidermis of atypical melanocytes that often have large nuclei and nucleoli and abundant pale cytoplasm. Mitoses are frequently absent. The melanocytes may be distributed singly or in nests. The distribution is often irregular and the nests may have irregular shapes or show confluence. Poor lateral circumscription is often present, with single enlarged melanocytes found lateral to the last nest. Hair follicles and eccrine duct epithelium can be involved in a similar pattern. To one side or in the subjacent dermis there may be a residuum of a naevus. In MIS the stromal and inflammatory reaction tends to be inconspicuous and can be absent. An irregular distribution of lymphocytes and/or melanophages may be a diagnostic clue that the lesion is a melanoma. Actinic elastosis may or may not be present. With development of invasive melanoma, an asymmetric outline becomes a major characteristic. Extensive and highly irregular junctional tumour nests are found at a variable distance to each

Fig. 2.13 Superficial spreading melanoma. A Low power magnification of the papular component. B Pagetoid spread of single melanocytes as is typically found in many examples.
other and may merge. There is often a lack of maturation, manifested by a failure of nests, cells, nuclei or nucleoli to become smaller towards the base of the lesion. Pigment is often irregularly distributed. Mitoses, sometimes atypical, are often seen whereas necrotic melanocytes are rarely identified. A lymphocytic infiltrate may be present at the base of the neoplasm or may infiltrate among its cells (so called tumour infiltrating lymphocytes or TILs). Melanoma may undergo regression, which clinically and grossly most often involves a portion of the lesion, or occasionally its entirety. Histologically this regression may be complete or partial within a given area. Complete regression of a portion of a melanoma ("segmental regression") is manifested by absence of melanocytes in the affected area. In partial regression, there is a strikingly diminished number of melanocytes compared to the remainder of the lesion. In both forms there is fibrosis of the papillary dermis, vascular proliferation and ectasia, and variably dense infiltrates of lymphocytes and melanophages. The epidermis may show loss of rete ridges. The type of regression described above affects the radial growth phase. Occasionally, a vertical growth phase may undergo regression, and sometimes the regressed portion may be replaced by a large mass of melanophages, representing a phenomenon called "tumoural melanosis".

**Immunoprofile**
There are no specific differences in the immunophenotype of SSM and other forms of melanoma.

**Somatic genetics**
SSM has a high incidence of mutations in the BRAF oncogene on chromosome 7q34 (1493). The most common chromosomal aberrations in SSM are losses of chromosomes 9, 10, 6q, 8p and gains of chromosomes 1q, 6p, 7, 8q and 20 (173). Melanomas with increased copies of chromosome 7 that show mutations of B-raf selectively increase the copy number of the mutated allele suggesting that the mutation precedes the chromosomal aberration (1493) The minimal deleted region on chromosome 9 includes the CDKN2A locus on 9p21 as can be seen by high-resolution comparative genomic hybridization (CGH) (876).

**Prognosis and predictive factors**
The prognosis of SSM does not differ significantly from other forms of melanoma (see Introduction).
Nodular melanoma

Definition
Nodular melanoma (NM) is a subtype of malignant melanoma (MM) exclusively in vertical growth phase.

ICD-O code 8721/3

Epidemiology
In most parts of the world, NM is the second most common subtype of MM, and accounts for 10 to 15% of all melanomas in Caucasian people (163,436). NM appears on the average, in older individuals than the common superficial spreading MM (SSM) (436,493).

Etiology
Most of the skin characteristics and risk factors associated with the development of NM are similar to those of SSM (1364), including fair or red hair, blue eyes, fair skin, tendency to develop freckles and sunburns, excessive exposure to ultraviolet radiation, numerous common naevi, giant congenital naevi, atypical (dysplastic) naevi, melanoma in a first degree relative, familial atypical mole-melanoma syndrome, immunosuppression, xeroderma pigmentosum and prior melanoma (624,2304).

Localization
NM may occur in any location, but as for SSM, it is more common on the trunk, head and neck, and lower legs (163).

Clinical features
NM typically present as a rapidly expanding papule, nodule or plaque. They are occasionally polypoidal and even pedunculated. They are usually well circumscribed and symmetric and frequently reach a size of approximately 1 cm before diagnosis. The skin markings are often obliterated with frequent ulceration and crust. The colour is often black or blue, although a subset of NM is amelanotic. The amelanotic variety frequently has a subtle blush or peripheral rim of pigment (163,436).

Macroscopy
As in the clinical features.

Tumour spread and staging
The tumour spreads first to the local lymph nodes and then to internal organs. The staging system devised by the American Joint Committee on Cancer includes aspects of the primary tumour, the status of lymph nodes, and the presence and location of any metastases (TNM staging) (130).

Histopathology
Scanning magnification discloses a raised, dome-shaped, or polypoid tumour, often, but not always, exhibiting some asymmetry. The overlying epidermis may be thin, effaced or ulcerated. Melanoma cells may be present in the overlying epidermis but not beyond the margins of the dermal component (some allow an extension up to 3 adjacent epidermal rete ridges beyond the dermal component). The dermal component is typified by a cohesive nodule or small nests of tumour cells that have a “pushing” or “expansile” pattern of growth. The tumour cells most frequently are epithelioid, but other cell types, including spindle cells, small epithelioid cells resembling naevus cells, and giant mononuclear or multinucleate forms, may predominate or be admixed with other cell types. The cell population usually appears monomorphous but closer examination reveals frequent cellular enlargement, nuclear enlargement, variation in nuclear size and shape, hyperchromatism, and prominent nucleoli.

Fig. 2.15 Nodular melanoma. A On scanning magnification the tumour has a polypoid configuration with slight asymmetry. Cohesive nodules of tumour cells fill the dermis. B Superficial portion of the tumour. Epithelioid melanoma cells are present as single units and in nests that vary in size and shape along the dermoepidermal junction and above it. Similar nests are present in the upper dermis along with numerous melanophages and lymphocytic infiltrates. Some of the epithelioid melanoma cells contain fine melanin granules.

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S. Brückner-Tuderman
J. Hercogova
B.C. Bastian
High nuclear-to-cytoplasmic ratios are often noted. The tumour cells fail to “mature” with progressive descent into the dermis. The cytoplasm of the epithelioid cells often has eosinophilic granular qualities. It may contain melanin granules that vary in size, or appear fine and “dusty”. There is absence of melanin in the amelanotic tumours. The surrounding stroma may demonstrate variable mononuclear cell infiltrates, fibroplasia, telangiectasia, and melanophages.

**Immunoprofile**
S-100 protein, HMB-45, Melan A (MART-1), MAGE-1, NKI/C-3, tyrosinase, melanoma cell adhesion molecule (MelCAM) MUC18 and microphthalmia transcription factor (MITF), are expressed by most melanomas (732,1500,1855). Melanoma cells also express bcl-2 protein, neuron specific enolase and vimentin (626,1861,2131). Antigens which may demonstrate higher rates of expression in melanoma cells than in naevoid cells include Ki-67 (MIB-1), proliferating nuclear antigen (PCNA), p53, cyclin D1, and p21 WAF1(9). The loss of expression of CDKN2A (cyclin dependent kinase inhibitor), and the increased expression of \( \beta3 \) integrin, have been associated with vertical growth phase and more invasive forms of melanomas (1029,1500,1904,2277,2278,2406).

**Electron microscopy**
The demonstration of stage II melanosomes is the hallmark of melanoma diagnosis. They are rarely found in other tumours. Other frequent findings are nuclear pseudoinclusions, prominent nucleoli and cytoplasmic intermediate filaments corresponding morphologically to vimentin filaments. In a minority of melanomas poorly developed intercellular junctions may be present (1016).

**Precursor lesions and histogenesis**
It is more common for NM to begin de novo than to arise in a pre-existing naevus (163). One hypothesis holds that NM represents a final common pathway of very rapid tumour progression from a brief intraepidermal proliferative phase of SSM, lentigo maligna, or acral lentiginous MM (154,163).

**Somatic genetics**
Comparative genomic hybridization and mutation analyses have revealed marked differences between melanomas depending on the anatomic site and sun-exposure patterns (173,1493). These studies did not find unique genetic features in nodular melanomas that justify regarding them as a unique type, supporting the ‘common pathway hypothesis (154,163).

**Prognosis and predictive factors**
In the T (tumour) category, tumour thickness increased mitotic rate and ulceration are the most powerful predictors of survival, and the level of invasion has a significant impact only within the subgroup of thin (\( \leq 1 \) mm) melanomas (131). Other adverse prognostic factors include increased tumour vascularity, vascular invasion, microscopic satellites, male gender, increased age, and anatomic location on the head, neck and trunk (122,1528,2597). In the N (nodes) category the following three independent factors have been identified: the number of metastatic nodes, whether nodal metastases were clinically occult or clinically apparent, and the presence or absence of primary tumour ulceration. In the M (metastases) category, nonvisceral metastases are associated with a better survival compared with visceral metastases (131).
Lentigo maligna

Definition
Lentigo maligna (LM) is a form of melanoma in situ that occurs on the sun exposed skin of elderly people, mainly on the face but also, less often, at extrafacial sites including the neck, upper back and forearm. It is characterized histologically by linear and nested proliferation of atypical melanocytes along the dermo-epidermal junction and down the walls of hair follicles and sweat ducts. The melanocytic lesion is associated with severe actinic damage, manifested by epidermal atrophy and solar elastosis. When dermal invasion by atypical melanocytes occurs in association with (LM), the term lentigo maligna melanoma (LMM) is used.

ICD-O code 8742/2

Synonyms and historical annotation
LM has also been known as Hutchinson melanotic freckle, after Hutchinson first described it as “senile freckle” in 1892 (1090) and subsequently as “lentigo melanosis” (1089). Dubreuilh (652) described these lesions as “mélanoise circonscrite précancreuse” which subsequently came into common use as melanosis circumscripta precancerosa until the classification of Clark (492) in 1967 introduced the category of melanoma commencing in lentigo maligna (Hutchinson’s melanotic freckle). That classification was widely but not universally accepted; the World Health Organisation (WHO) classification of 1974 classified superficial spreading melanoma and melanoma arising in Hutchinson melanotic freckle (lentigo maligna melanoma) in one category (2337). The World Health Organization (WHO) classification of 1996 separated melanoma in-situ into superficial spreading or pagetoid type and lentigo maligna melanoma, whilst acknowledging that there may be no essential biological difference between some or perhaps all categories of melanoma (999).

Etiology
The strong association between LM and its occurrence in the severely sun damaged skin of elderly people has been widely accepted as evidence that LM and LMM represent a distinctive form of melanoma, resembling etiologically the non-melanocytic skin cancers, and suggesting that LM arises in response to accumulated sun exposure, in contrast with the more common forms of melanoma that appear to be related to intermittent sun exposure (1048). It has also been suggested, however, that differences in body site distribution between the commonly accepted different types of melanoma, through their interaction with amount and pattern of sun exposure, can explain virtually all the observed pathological and epidemiological differences between LM and the more common types of melanoma that occur in widespread anatomical distribution (16,996). Recent studies have found that LM remains the main histologic type of melanoma in situ on the head and neck and that patients with LM are less likely than patients with melanomas of the trunk to have more than 60 naevi whereas they had a stronger association with the number of solar keratoses (2508).

Pathogenesis
According to some authorities, the term LM encompasses a phase regarded as a melanoma precursor in which there is proliferation of melanocytes in severely sun damaged skin in intermittent pattern without the confluent growth, pagetoid spread and nesting of atypical melanocytes that, according to this concept, represent malignant melanoma in-situ of LM type, whereas the lesions with less severe, intermittent junctional proliferation are termed atypical melanocytic hyperplasia (759) or, preferably, atypical lentiginous melanocytic proliferation.

Localization
Head and neck are by far the most common sites in both sexes. Extrafacial LMM differs in its site distribution between women and men (549). A study in Scotland showed that extrafacial LMM in men occurred mainly on the trunk whereas in women 80% occurred on the limbs, mainly the lower leg. The mean age of patients with extrafacial LMM was significantly lower than that of patients with head and neck LM, suggesting that the association between LMM and sunlight may not be related only to the cumulative effects of solar exposure.

Clinical features
LM may be recognized as a small lesion, usually as a mottled light brown macule with irregular margins on the face of a fair skinned elderly patient with evidence of severe solar skin damage, only a few millimetres in diameter, but usually greater than 10 mm. The classical lesions are broad, flat zones of varied pigmentation with an irregular border. With increasing size of the lesion, variation in pigment and irregularity of the border also...
become more pronounced, nodules may develop within the lesion and the borders may become difficult or impossible to define where zones of pallor or mottled pigmentation merge imperceptibly with the surrounding skin.

**Histopathology**

LM is characterized by a predominantly junctional proliferation of atypical melanocytes, frequently extending down the walls of hair follicles and sweat ducts, in association with epidermal atrophy and severe solar elastosis. Although the junctional proliferation may form confluent linear pattern in some areas, elsewhere the atypical melanocytes may be distributed as single units separated by basal cells. Irregular junctional nests of atypical melanocytes are frequently present, as are multinucleate giant cells including those of starburst type (512). Marked pleomorphism is a feature of the atypical melanocytes which show cytoplasmic retraction artefact and nuclei of stellate, ovoid and crescentic forms, some of them pressed against the cell wall, with a variable chromatin pattern and clear or variably pigmented cytoplasm. Pagetoid foci of atypical epithelioid melanocytes present an appearance indistinguishable from melanoma in situ of so-called superficial spreading type.

A lymphocytic infiltrate and focal fibroplasia are frequently present in the papillary dermis underlying LM, with severe solar elastosis and telangiectasia. Regression, shown by fibrosis, hypervascularity, melanophages and a patchy lymphocytic infiltrate, is a common feature and should prompt a careful search for invasion by atypical melanocytes. The presence of regression at a lateral margin of excision should be emphasized in the report as an indication for re-excision, even when the margins appear clear of atypical melanocytes.

In LMM, dermal invasion occurs in association with LM. The invasive component may consist of atypical melanocytic spindle cells more frequently than is seen in the other common forms of cutaneous melanoma, but epithelioid, small naevoid and tumour giant cells may also be present in varied proportions. The cells of these various types may occur in cohesive groups, strands or as single cells in a diffuse pattern, often associated with lymphocytes and melanophages. The degree of pigmentation varies, including cells with abundant clear cytoplasm adjacent to cells in which the morphologic detail may be obscured by coarse melanin granules.

The invasive component in LMM may be desmoplastic and/or neurotropic with very subtle, diffuse invasion that predisposes to incomplete excision and true local recurrence. Dermal invasion may also originate from atypical melanocytes in the walls of hair follicles and sweat ducts, thus creating a problem in measurement of tumour thickness because it is inappropriate to measure tumour thickness from the granular layer of the epidermis in this instance.

The degree of pigmentation in LM may vary markedly between different examples of the tumour and within one tumour. Zones of amelanosis at the periphery of the lesion may lead to failure by the pathologist to detect atypical cells at the margin of excision, thus leading to persistent growth and “local recurrence” of the tumour.

**Differential diagnosis**

In cases of extensive amelanosis (amelanotic LM) (60), the distinction between in-situ squamous cell carcinoma or extramammary Paget disease may be difficult in routine sections, necessitating the use of special stains to demonstrate epithe-
Histogenesis
LM develops from epidermal melanocytes, most likely due to the cumulative DNA damage resulting from long-term sun exposure (1048). A recent study of the differential expression of proliferation- and apoptosis-related markers in lentigo maligna and the keratinocytes in solar keratosis has found that the epidermis in LM shows overall low proliferation and a low apoptotic tendency, perhaps aiding aberrant melanocyte proliferation in the early stages of melanoma development (718).

Somatic genetics
A recent study has shown an association between DNA repair-deficiency and a high level of TP53 mutations in melanomas of xeroderma pigmentosum patients (2231). The LMM found in xeroderma pigmentosum patients of the XP complementation group, group XP-C, were associated with an accumulation of unrepaird DNA lesions. Lentigo maligna melanomas have been found to rarely show mutations in BRAF (1493). Comparative genomic hybridization shows more common losses involving chromosome 13 and less common losses of chromosome 10, when compared to other melanoma types (173).

Prognosis and predictive factors
Complete excision of lentigo maligna, as a form of melanoma in situ and, therefore, incapable of metastasis, is curative. Prognosis for LMM has been a contentious issue. For many years, it was commonly believed that the prognosis for melanomas of LMM type is better than for other types of melanoma. Most evidence, however, suggests that for melanomas classified as different types according to their histological features, their differences in survival correspond to differences in tumour thickness rather than to their differences in histologic type (20,1296).
Acranal-lentiginous melanoma

Definition
Acranal lentiginous melanoma (ALM) is a distinct variant of cutaneous melanoma, which occurs on the palms, soles, and subungual sites, and has a characteristic histologic picture. Following the three other major clinicopathological subtypes of melanoma, i.e. superficial spreading melanoma, lentigo maligna melanoma, and nodular melanoma, ALM was proposed as the fourth subtype by Reed in 1976 (1905). In this article, we also use the term acral melanoma and define it as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails. The reason for this usage is described below.

ICD-O code 8744/3

Synonyms
Historically, this type of melanoma has been designated as ALM (1905), acral melanoma (494), palmar-plantar-subungual-mucosal melanoma (P-S-M melanoma) (2129), or unclassified plantar melanoma (100). Although often considered to be interchangeable, ALM and acral melanoma embody distinct concepts that must be distinguished from each other. ALM is a histologic designation that shows similarities to lentigo maligna melanoma, while acral melanoma is an anatomic designation that refers to melanoma located on the acral sites. Acral melanoma, thus, encompasses both ALM and such subtypes as superficial spreading melanoma and nodular melanoma that may develop in acral locations. Occasionally, the terms acral melanoma and acral lentiginous melanoma are used interchangeably, since the majority of cases of acral melanoma are ALM (1071,1592,1905) and the histological distinction between ALM and superficial spreading melanoma is not always possible (2220). Even if acral melanoma is an anatomic nomenclature, its use is different among articles. We define it as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails because of presentation of the genetic data. Although P-S-M melanoma was described on the basis of clinical and histologic similarities between the tumours on these sites, the acral melanomas and mucosal ones are recommended to be treated separately, because of their different clinical behaviours (494).

Epidemiology
Racial differences are quite pronounced in the incidence and predilection sites of melanomas. This is particularly true for acral melanoma wherein acral melanoma comprises 2% and 80% of cutaneous melanomas in Caucasian and dark-skinned patients respectively. In a German study approximately 7% of patients with cutaneous melanoma had...
tumours located on acral sites (1337). Whereas 77% of cutaneous melanoma in Japanese patients occurs on acral sites (2130). In African and African-Americans, the highest incidence of cutaneous melanoma has been reported on relatively non-pigmented areas, such as the soles, nail plates, and mucous membranes (1417). Thus, ALM is the most common type of melanoma in dark-skinned peoples and Asians (1268, 2129). Nevertheless the absolute incidence of acral melanoma in dark-skinned African and light-skinned Caucasian populations in North America is similar, suggesting that the observed racial difference may relate to a decreased incidence of non-acral melanoma in African American populations (2268). Compared with the escalating incidence that typifies other melanoma subtypes, the incidence of ALM has remained static (661).

Overall, ALM occurs in an older patient population than does superficial spreading or nodular melanoma, and, in populations where ALM is common, this tumour more often afflicts men than women. Overall, the age distribution of ALM is similar to that of lentigo maligna melanoma, peaking in the seventh decade of life, whereas superficial spreading melanoma and nodular melanoma peak in the sixth decade (1337). The mean age of ALM ranges from 55 to 68 years in European countries (767,1337,2123). In Japanese patients, there is a peak in the sixth decade in both males and females. In Japan, Korea, and Taiwan, men are effected twice as often as women (1220, 1268,1428,2130). On the other hand in western countries, there is less of a male predominance in patients with ALM (1337,2220).

Localization
The term acral has been used differently throughout the literature. Most publications use acral for the non-hair bearing, i.e. glabrous skin of the palms and soles, and the nail bed, whereas others also include the dorsal aspect of the hands and feet under this term. In a German study, using the latter definition, acral melanoma occurred on the feet in 87% cases (plantar sites, 57%; subungual, 5%; and dorsum, 9%) and on the hands in 23% (palm, 1%; subungal, 14%; and dorsum, 9%) (1337). Thus, the plantar sites were greatly more often affected than the palmar sites (1337,2130,2201,2220,2296). In contrast to ALM, superficial spreading melanoma occurs more commonly on the sun-exposed dorsal aspects of the hands and feet, whereas nodular melanoma occurs on all acral sites with relatively equal frequency (1337). In addition to the sole, nail plate is an especially frequent site with a frequency of 16-19% in ALM (1337). In contrast to ALM, superficial spreading melanoma occurs more commonly on the sun-exposed dorsal aspects of the hands and feet, whereas nodular melanoma occurs on all acral sites with relatively equal frequency (1337). In addition to the sole, nail plate is an especially frequent site with a frequency of 16-19% in ALM (1337,2130). In contrast to the palmar/plantar melanomas, subungual melanomas occur more often on the hands than on the feet (745,1221,2130,2315). In the Japanese series, the number of subungual melanomas on the fingers is 62-72% and on the toes 28-38%, with an 82% incidence on the thumbs and great toes (1221,2130). The high percentage of occurrence on the thumbs and great toes may suggest a role for trauma in the etiology of subungual melanoma (2130). Since sun exposure obviously plays little role in palmoplantar sites, the causative role of ultraviolet light is presumed to be negligible in ALM.

Clinical features
Acral melanomas in the early stages appear as a pigmented macule similar to lentigo maligna. Acral melanomas commonly exhibit clinical evidence of a biphasic growth pattern, with a more rapid evolution from an entirely flat clinical lesion to a lesion containing an elevated focus than is observed in the other types of melanoma. The radial growth phase of ALM is characterized by a macular pigmented lesion with highly irregular, notched borders and varying shades of pigmentation. Within a background pigmented macule, acral melanomas often develop a clinically apparent vertical growth phase. This is manifest as an elevated papule or nodule, sometimes with a verrucous surface, and corresponds to the histological vertical growth phase of malignant melanocytes. Ulceration is more often seen in ALM than in other types of melanoma. Subungual melanomas often begin as brown to black discolouration of the nail that frequently become bands or streaks of pigmentation. Thickening, splitting, or destruction of the nail plate may occur. The irregular macular hyperpigmentation, coloured tan to dark brown, is also recognized around the nail plate (2130). In one study, 17% of the patients noticed
the pre-existence of some pigmented skin lesions, and 21% related a history of trauma (2130). Pigmented streaks are not uncommon in patients with deeply pigmented skin, nevertheless, a history of a new or recently changing pigmented lesion should prompt the consideration of a biopsy for histological evaluation of the lesion. In this case, reflection of the proximal nail fold to enable biopsy of the nail bed may be necessary for definitive diagnosis. Unfortunately, clinical misdiagnosis is not uncommon in patients with ALM (409, 767, 1327, 1592, 2222). Therefore, awareness of atypical presentations of ALM that may contribute to misdiagnosis or diagnostic delay assumes particular importance. ALM lesions are frequently treated or followed for considerable time under the clinical diagnosis of wart, cal- lus, fungal disorder, subungual haematoma, keratoacanthoma, nonhealing ulcer, foreign body, naevus, ingrown toenail, etc (2222).

**Histopathology**

The histology of ALM is characteristic but not distinct. In the radial growth phase, the lesions are characterized by marked acanthosis, expanded cornified layer, elongation of the rete ridges, and lentiginous proliferation of atypical melanocytes along the basal epidermis at the border of the tumour (1337, 1767). The intraepidermal component of acral melanoma includes large, atypical melanocytes with large, often bizarre nuclei and nucleoli, and cytoplasm filled with melanin granules (2130). These melanocytes in the basal layer often exhibit long, elaborate dendritic processes (2130).

Atypical melanocytes can extend along the sweat ducts into the deep dermis. In the vertical growth phase, tumour nodules often contain predominantly spindle-shaped cells and are associated with a desmoplastic reaction (2130). The junc- tional component of thicker tumours often shows nesting of tumour cells and upward migration to the cornified layer (1337).

**Immunoprofile**

As in the other types of melanomas, immunohistochemical stainings for S-100 protein, HMB-45, and MART-1 (also known as Melan-A) are of great diagnostic value in ALM. S-100 protein (positive cases, 95%) is a more sensitive marker than either HMB-45 (80%) or MART-1 (70%) (1268). However, S-100 protein-negative ALM has been reported (83). The intensity of HMB-45 but not of S-100 protein is correlated well with the melanin content. HMB-45-negative cases are all amelanotic, but amelanotic cases are not all negative for HMB-45 (1268). The melanoma cells also express vimentin (1268). Focal staining for CAM5.2 or epithelial membrane protein may occasionally be found (1268).

**Somatic genetics**

Comparative genomic hybridization (CGH) of melanomas on acral non-hair bearing skin showed distinct differences to melanomas on non-acral skin (171). A study of 15 acral melanomas and 15 superficial spreading melanomas from non-acral sites showed that all (100%) acral cases had gene amplifications, whereas amplifications were found in two of the superficial spreading melanomas (13%). The most common amplified region is chromosome 11q13 which occurred in 50% of these types of melanoma. A recent study has shown that cyclin D1 is one of several candidate genes in this region. This conclusion was based on the observation that amplification of the cyclin D1 gene was always accompanied with overexpression of the cyclin D1 protein, and that inhibition of cyclin D1 expression in vitro and in xenograft models led to apoptosis or tumour shrinkage (2072). FISH studies on primary lesions of acral melanoma showed that the amplifications arise early in acral melanoma and can already be detected at the in situ stage (171). The *in situ* portion of acral melanoma may extend beyond what is recognizable histopathologically. FISH detected gene amplifications were identified in single basal melanocytes immediately adjacent to the in situ component of acral melanoma; they were equidis- tantly spaced and looked histopathologically inconspicuous (171). Based on the observation that these “field cells” were found at the histopathologically uninvolved excision margins of an acral melanoma that recurred multiple times the authors propose that field cells may be a form of minimal residual melanoma that leads to persistence if not removed. More recent studies using array CGH have confirmed the frequent gene amplifi-

**Prognosis and predictive factors**

In general, the prognosis of invasive acral melanoma is poor. This can partly be explained by the above described diagnostic delay and increased tumour thickness at the time of diagnosis. However, there are some studies sug- gesting that acral melanomas may undergo a more aggressive course independent of tumours thickness (151, 308, 661, 1337). In a study from Germany, 63 out of 64 patients (98.5%) with melanoma of the sole subsequently developed metastases (775); a corresponding fig- ure from Japan in 1983 was 35% (2130). The same hospital recorded that the 5- year survival rate of subungal melanoma increased from 53% in 1969-82 to 83% in 1983-93 (1221), presumably because of early awareness of lesions and development of treatment (2012). However, others have reported that ALM is not a sig- nificant prognostic indicator (661, 2201), and adjustment for histologic and clinical stage renders the prognostic importance of anatomic location insignificant (151, 308). These conflicting results can in part be explained by the different definitions used for acral melanomas in the studies. Future studies using refined criteria including genetic information are neces- sary to assess the prognosis of this melanoma type.

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**Acral-lentiginous melanoma** 75
Definition
Desmoplastic melanoma (DM) is a spindle cell melanoma in which the malignant cells are separated by collagen fibres or fibrous stroma. It displays variable cytological atypia, cellularity and stromal fibrosis and more often than not has an accompanying junctional component. Neurotropism is a common associated feature (in at least 30% of cases) and when it occurs such tumours are termed desmoplastic neurotropic melanomas (DNM). The neurotropism may be perineural or intraneural and often extends beyond the desmoplastic component. DM may also present as a recurrence or occasionally as a metastasis from other types of melanoma.

ICD-O code 8745/3

Historical annotations
DM was first described by Conley et al. in 1971 (526) as a clinically inconspicuous superficial melanocytic lesion, mainly on the head and neck, with an atypical junctional component, preceding the development of a bulky dermal and subcutaneous tumour. The latter was composed of atypical melanocytes and spindle cells often with elongated nuclei and a dense collagenous ground substance. Many others subsequently highlighted the frequent neurotropism of DMs.

Epidemiology
Desmoplastic melanomas represent between 1-4% of melanomas. In a large series from the Sydney Melanoma Unit...
Desmoplastic melanoma and desmoplastic neurotropic melanoma

(SMU) the median age at diagnosis was 61.5 years (range 24-91) \(1867,1868\). As in other histogenetic types of melanoma, males are more often affected \(M:F = 1.75:1\) \(358A,1867,1868\).

**Etiology**
The etiology is unknown, but the majority occurs in sun-exposed skin. Some have occurred in irradiated areas \(1125\).

**Localization**
DM may be found in many sites but most commonly involves the head and neck region \(37%\), including ear, nose and lip \(1077\). Males predominate except on the lower limbs. The vulva is a rare site for DM \(1664\).

**Clinical features**
Most present as a painless indurated plaque but some begin as a small papule or nodule \(2501\). Almost half lack pigmentation \(1867\). Pale lesions are often mistaken for basal cell carcinoma, dermatofibroma or a scar. Pigment is usually due to an associated lentigo maligna (LM)/Hutchinson melanotic freckle (HMF) or superficial spreading melanoma. Unusual presentations include a young age \(439,1077\), an erythematous nodule \(1326\) and alopecia \(563\).

**Macroscopy**
Ulceration is uncommon although it was found in 17% of the SMU cases \(1868\).

**Tumour spread and staging**
The tumours usually infiltrate deeply into the reticular dermis but local spread may involve subcutaneous tissue, deep fascia including periosteum and pericranium, bone and salivary gland. Neurotropic foci may be found well beyond the main tumour. In the SMU series, neurotropism was found only in tumours exceeding 1.5 mm in thickness and Clark level 4 or 5 \(1867,1868\). Initial metastases from DM may involve regional lymph nodes or distant sites.

**Histopathology**
In DM the spindle-shaped melanocytes, which often resemble fibroblasts and are usually non-pigmented, are found in and between mature collagen bundles. The latter may be thickened and/or associated with a mild to marked stromal fibrosis. The distribution of spindle cells is usually haphazard but occasionally they form parallel bundles or storiform areas. The spindle cells often extend into the subcutis diffusely or in fibrous bands and may involve deep fascia, especially pericranium. The overlying epidermis may be thinned or thickened. Characteristically there are accompanying small islands of lymphocytes and plasma cells within and/or at the edge of the tumour. The cytological atypia of the spindle cells usually varies from mild to moderate. However, even in cases with mild atypia, there are usually a few larger or more elongated hyperchromatic nuclei. The cytoplasm of the spindle cells is often poorly defined. In examples where the spindle cells are small, well scattered and associated with solar elastosis, the lymphoid islands may be the main clue to the diagnosis. Paucicellular variants are easily missed on punch and shave biop-

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**Fig. 2.23** Desmoplastic melanoma. **A** Male, 57 yrs, upper lip. Abnormal junctional melanocytes, spindling dermal melanocytes and a patchy lymphocytic infiltrate. **B** Female, 76 yrs, forearm. Abnormal junctional melanocytes and dermal spindle cells with patchy lymphocytes.

**Fig. 2.24** Desmoplastic melanoma. **A** The spindle cells stain poorly with S100 unlike the Langerhans cells and interdigitating cells. **B** Variable S-100 positive nuclear and cytoplasmic staining. **C** Crowded abnormal spindle cells and atypical mitoses.
Melanocytic tumours

Melanocytic tumours

negative. Microphthalmia transcription positive. Melan A (MART-1) is usually and smooth muscle actin {1929} may be epithelioid cells {2476}. NSE, NKI/C-3 usually negative except for any foci of some otherwise typical cases. HMB45 is although only a few nuclei are positive in the spindle cells. The spindle cells are positive with S-100 Immunoprofile

sary for the diagnosis of DM has been ill described. The proportion of desmoplasia in a melanoma necessary for the diagnosis of DM has been ill defined in several studies, but proposals for diagnostic criteria have been made {358A,985A,1546A}. Metastases in lymph nodes may be epithelioid cells, or spindle cells with or without desmosplasia. Melanomas of any histogenetic type may have desmoplastic areas. The proportion of desmoplasia in a melanoma necessary for the diagnosis of DM has been ill defined in several studies, but proposals for diagnostic criteria have been made {358A,985A,1546A}. Metastases in lymph nodes may be epithelioid cells, or spindle cells with or without desmosplasia.

Immunoprofile

The spindle cells are positive with S-100 although only a few nuclei are positive in some otherwise typical cases. HMB45 is usually negative except for any foci of epithelioid cells {2476}. NSE, NKI/C-3 and smooth muscle actin {1929} may be positive. Melan A (MART-1) is usually negative. Microphthalmia transcription factor (MTF) is not a sensitive or specific marker {356,885,1294}. Type IV collagen and laminin are frequently expressed in DM {1857}. Vimentin is usually positive although positive staining does not usually assist in diagnosis.

Differential diagnosis

The differential diagnosis includes desmoplastic naevus {958}, which like DM may have perineural extension but lacks asymmetry, mitotic activity, marked nuclear atypia and lymphoid infiltrates. Well established desmoplastic Spitz naevi may have many HMB45 negative spindle cells but these nevi are usually symmetrical with epidermal thickening, include at least a few plump cells and have rare or absent mitoses. Sclerosing cellular blue naevi, which are most frequent on the scalp, also lack mitoses and are more or less diffusely HMB45 positive. Immature scars, especially in re-excision specimens, may focally resemble DM as they may have some S-100 positive spindle cells {476,1951}, foci of lymphocytes and mitoses. Other differential diagnoses include dermatofibroma/fibrous histiocytoma, fibrosarcoma, “malignant fibrous histiocytoma”, malignant peripheral nerve sheath tumour and leiomyosarcoma. These tumours can usually be separated by morphology and appropriate immunohistochemistry.

Histogenesis

It is most likely that the desmoplastic cells are derived from melanocytes that have undergone adaptive fibroplasia. Some authors have suggested that the desmoplasia occurs because of a fibroblastic stromal response and neurofibrosarcomatous differentiation of the tumour cells {2476}. Ultrastructurally, premelanosomes and melanosomes are rare and the spindle cells have the features of fibroblasts. There is abundant rough endoplasmic reticulum and sometimes intracytoplasmic collagen and macular desmosomes {2476}.

Somatic genetics

Chromosomal aberrations and gene mutations have been found in sporadic and familial melanoma {799}. Allelic loss at the neurofibromatosis type 1 (NF1) gene locus is frequent in DM {931}. Basic fibroblast growth factor (bFGF) and other fibrocytokines are often present in the nuclei of DMs {1335}. Loss of heterozygosity of matrix interacting protein 1 (MXI1) is frequent {1893}. No BRAF mutations were found in 12 desmoplastic melanomas {596}, consistent with the finding that melanomas on chronically sun-exposed skin only rarely have BRAF mutations {358B,596,1493}.

Prognosis and predictive factors

Recurrences are common especially after incomplete excision {526}, marginal excision <10 mm or if neurotropism is present {1867,1868}. The conflicting results regarding the risk of regional node field metastases and prognosis of DM patients may be due to a heterogeneity of tumours classified as DM and failure to account for tumour thickness {2115A}. Regional nodal metastases appear to be uncommon in paucicellular DMs with prominent fibrosis and are associated with longer survival {358A,932A,985A}. Otherwise, disease free survival rates are similar to other melanomas of comparable thickness {126}. Neurotropism, HMB45 positivity, high mitotic rate, male gender, thickness, ulceration and site all appear to affect survival which overall is 79% at 5 years {1868}. Of patients with a recurrence, 78.2% experienced it within 2 years. Wide local excision is the treatment of choice {99A}. Radiation therapy has been effective in some cases {71,1125}.
Melanoma arising from blue naevus

L. Requena
J. A. Carlson

Definition
A melanoma that arises in association with dermal melanocytosis, most frequently cellular blue naevus.

Synonyms
“Malignant blue naevus” or “blue naevus-like melanoma” are terms used to describe melanomas arising in association with a cellular blue naevus or those primary melanomas that resemble blue naevi and lack an in situ component.

ICD-O 8780/3

Epidemiology
Melanoma associated with blue naevus is an exceedingly rare tumour with over 165 reported cases. It affects predominantly Caucasians and all age groups with the majority of cases occurring between 20 and 60 years, with a mean age at diagnosis of 44 years (2066, 2332). Slightly more females than males have been reported (82 females; 76 males). Occasionally, dark-skinned patients develop melanoma in association with a blue naevus (548,1352,1629).

Localization
In decreasing order, the sites most frequently affected are the scalp (33%), orbit and face (32%), trunk- mostly back and buttocks (19%), extremities (7%) and hands or feet (7%). Involvement of the vulva and vagina have also been reported (422,2233).

Clinical features
Most melanomas associated with blue naevus (93%) develop in a pre-existing dermal melanocytosis that was congenital (35%), acquired during infancy or childhood (15%) or identified during their adult years (43%). These associated lesions were cellular blue naevi (52%), common blue naevus (16%), naevus of Ota (14%), naevus of Ito (1%) (2066, 2414), or ocular melanocytosis (542, 1127,2332,2431). On average, these melanocytoses were present for 24 years before melanoma developed, with a range of 3 months (infant with congenital facial blue naevus (2066)) to 78 years (naevus of Ito (2414)). For congenital and childhood onset melanocytoses, melanoma developed after a mean duration of 34 years (range 3 months to 78 years) whereas for adult onset common or cellular blue naevi, melanoma developed on average after 14 years (range 1 – 56 years). The majority (83%) of affected patients described recent, often rapid, growth or presented with proptosis in the case of orbital melanomas within a year of diagnosis. Other symptoms include colour change or ulceration, and in the case of orbital melanomas, diplopia and blurred vision. The melanoma is typically a large black nodule with mean diameter of 2.1 cm (range 0.5–8.0 cm). In some cases, satellitosis due to cutaneous metastatic deposits appear around the primary nodule (64,276,364,856,1018, 1588,1981,2066). However, this feature can also represent the well-known phenomenon of satellitosis associated with the common and cellular blue naevus (agminated blue naevus) (616,1059, 1195,2008). Similarly, cellular blue naevus can also present with regional lymph node deposits (143,1357,2261). In the former cases, histopathologic examination of the satellite lesions reveals features of benign blue naevus and the lesions present benign biological behaviour with no development of distant lesions.

Etiology
The etiology of melanoma associated with blue naevus is unknown, but the presence of longstanding dermal melanocytosis is likely a risk factor. Ocular and oculodermal melanocytosis (naevus of Ota) is strongly associated with uveal melanoma (2192,2193) and has been reported with meningeal melanocytoma (blue naevus) of the brain (1877) and primary melanomas of the central nervous system (253,569,1104, 1713,1930,2046). Based on this association and numerous reports of melanoma of the face, orbit or brain associated with oculodermal melanocytosis patients presenting with naevus of Ota should be considered at lifetime risk for melanoma of the skin, orbit or central nervous system, a risk that may be similar in nature to that identified for large congenital melanocytic naevi with melanoma and neurocutaneous melanocytosis (254).
Additional associations of unknown influence include subacute cutaneous lupus erythematosus, leukoderma, Becker’s naevus and prostate adenocarcinoma in one patient (1629), papillary thyroid carcinoma (94), acute lymphocytic leukaemia (2119), psoriasis (238), and oral contraceptives (1404). Phototherapy has been associated with cellular blue naevus development (810).

**Histopathology**

By definition, a melanoma that develops in a pre-existing blue naevus is a dermal melanoma without the features of melanoma in situ involving the dermoepidermal junction or adnexal epithelium. In fact, 82% of all reported cases described an adjacent common and/or cellular blue naevus. The absence of an identifiable benign naevus component in some reports may be the result of replacement of it by the melanoma or incomplete sampling of the benign element. Although these cases could represent de novo melanomas, a subtle, hypocellular dermal melanocytosis as seen in naevi of Ota and Ito, and ocular melanocytoses attest to this latter possibility of under-reporting (542,660,1783, 2332,2414).

At scanning magnification, two histopathologic patterns are evident. One is represented by the benign component of the blue naevus, which may range from very focal to comprising the main bulk of the neoplasm. Often this benign component is represented by a cellular blue naevus and less frequently the lesion contains a common blue naevus. Most cases, however, show a combination of the so-called cellular and common blue naevi, making this distinction useless. The areas of cellular blue naevus consist of solid aggregations of closely arranged monomorphous ovoid cells with abundant pale cytoplasm containing little or no melanin and round vesicular nuclei with inconspicuous nucleoli. In contrast, the areas of common blue naevus are made up of elongated spindled bipolar melanocytes, with long branching dendritic processes most of them filled with abundant granules of melanin. Melanophages and sclerotic bundles of collagen are also frequently observed between the fascicles of dendritic melanocytes. Although the malignant component may involve the superficial dermis and ulcerate the epidermis, more often it appears as a deep-seated expansile asymmetric nodule involving the reticular dermis and subcutaneous fat. Usually, there is an abrupt transition from the benign blue naevus component to the nodule of melanoma. The nodule or nodules of melanoma show both architectural and cytological features of malignancy. The melanomatous component consists of sheets of cells that involve diffusely the deep dermis destroying the pre-existing structures with pushing margins and sharp demarcation between the neoplasm and adjacent dermis or subcutaneous tissue. Neoplastic melanocytes appear as large spindled to epithelioid cells with abundant cytoplasm and pleomorphic and hyperchromatic nuclei, with prominent nucleoli and frequent mitotic figures. Usually they contain little or no melanin. Without the associated benign component, these dermal nodules would be histopathologically indistinguishable from typical nodular or metastatic melanoma. Necrosis of individual cells as well as necrosis en masse may be also seen in the melanoma component, although this finding seems to be less
frequent than in melanomas arising de novo ("malignant blue naevus") {973}. A perivascular inflammatory infiltrate, mostly composed of lymphocytes, which is usually lacking in blue naeves, is often seen around the melanoma arising in blue naeves. *Melanoma arising in the setting of blue naeves* should be differentiated from the so-called atypical cellular blue naevus (118,2371). These lesions show clinicopathologic features intermediate between typical cellular blue naevus and malignant melanoma associated with blue naeves. The lesions show architectural atypia, characterized by asymmetry and infiltrative margins, as well as cytologic atypia, which consist of hypercellularity, nuclear pleomorphism, hyperchromasia, mitotic figures and necrosis. However, follow-up data of patients with atypical cellular blue naevus demonstrated that no patient experienced either a local recurrence or lymph node or visceral metastasis.

Melanoma associated with blue naeves should be also distinguished from *large plaque-type or giant cellular blue naevus* with subcutaneous cellular nodules (358, 1059). Large pigmented plaques of childhood onset that show slow enlargement during adolescence and subsequent nodule formation clinically characterize this rare plaque variant of cellular blue naevus. Histopathologically, they exhibit multifocal dermal and subcutaneous proliferations of fusiform and dendritic pigmented melanocytes, with highly cellular nodules located in deeper areas of the plaque. The follow-up of patients with large plaque-type blue naeves with subcutaneous cellular nodules indicates that these lesions behave in a benign fashion.

**Metastatic melanoma mimicking blue naeves** can also be confused with melanoma associated with a blue naeves (354,2517). These blue-naeves like metastases occurred in the same anatomic region as the primary tumour or near the skin scar of a dissected lymph node metastasis and were histopathologically characterized by atypical epithelioid melanocytes, mitotic figures, and an associated inflammatory cell infiltrate at the periphery of the lesions. In contrast with melanoma arising in a pre-existing blue naeves, metastatic melanoma to the skin simulating blue naeves lacks the benign blue naeves component.

Animal type melanoma (*epithelioid melanocytoma*) is a rare variant of primary cutaneous melanoma that may also mimic melanoma associated with blue naevus (567,1917). Sheets and nodules of heavily pigmented epithelioid melanocytes that tend to aggregate along hair follicles and involve the entire thickness of the dermis with extension into the subcutaneous tissue histopathologically characterize animal-type melanoma. Epithelioid melanocytes in deeper areas show abundant, heavily pigmented cytoplasm and pleomorphic nuclei with prominent eosinophilic nucleoli and mitotic figures. Histopathologic features of melanoma in situ at the dermo-epidermal junction are few or absent, and neoplastic cells do not show evidence of maturation from superficial to deeper dermal areas. The overall architectural and cytologic features of animal-type melanoma closely resemble those of melanoma associated with blue naevus, but animal-type melanoma lacks the benign component of blue naevus or history of a pre-existing melanocytosis.

**Metastatic spread**

Melanoma associated with blue naevus is an aggressive tumour with frequent metastatic disease to regional lymph nodes (31% of reported cases) and distant sites (42%). Sites of metastasis, in decreasing order of frequency, include liver (36%), lung (22%), brain (16%), skin (13%), bone (9%), and in less than 6% of reported cases, spleen, heart, kidney, pancreas, adrenal, thyroid and parotid glands, ovary, and gastrointestinal tract. Melanuria and generalized melanosis have also been described in its terminal stage (2185). Metastases can appear as late as 20 years after diagnosis (813), but the median and mean time of discovery is 1.75 and 3.6 years after diagnosis. Metastasis to lymph nodes should be differentiated from the presence of blue naeves cells in the capsule of the node (181,392,405,1357,1358). This well-known pseudo-metastasizing phenomenon seems to be the result of migration arrest during embryogenesis and is characterized by monomorphic melanocytes of blue naevus involving only the capsule and the marginal sinuses of the lymph node. In authentic metastases, nests of atypical melanocytes replace most of the parenchyma of the node, effacing its architecture.

**Immunoprofile**

Immunohistochemical studies in lesions of melanoma associated with blue naeves have demonstrated a strongly positive reaction of the neoplastic cells, both of the benign and malignant components, for vimentin, S-100 protein, HMB-45 and NKI/C-3 (280,1708,1996). However, the number of silver positive nucleolar organizer regions (AgNOR score) (813,1826) and growth fraction as measured by proliferating cell nuclear antigen (PCNA) and Ki-67 (MIB-1) are significantly lower in the benign component of blue naevus than in the nodule of melanoma (1708,1826).

**Electron microscopy**

Although some authors have interpreted the neoplastic cells of melanoma associated with blue naevus as being related with Schwann cells (1588), electron microscopic studies have demonstrated the presence of melanosomes in the cells, as well as the lack of cytoplasmic enclosures of unmyelinated axons, which rule out the possibility of Schwann cell differentiation. Although the melanosomes in many cells of the malignant component are devoid of melanin (1014), incubation with dopa demonstrates that they are strongly dopa-positive (1625), thus confirming their melanocytic nature.

**Somatic genetics**

Results of DNA flow cytometry studies in melanoma associated with a blue naeves are variable revealing diploid cell populations in 4 cases (1574,1826) and aneuploid populations in 2 cases (1826). A molecular analysis failed to demonstrate loss of heterozygosity on microdissected samples in one case of melanoma associated with blue naevus, using a panel of eight genes (MTS1, MX1, OMM1, p53, NF1, L-my, hOGG1, and MCC), many of which are commonly associated with conventional melanomas (94). These findings suggest that melanoma associated with blue naevus may represent a distinct entity with a different molecular pathway to tumourigenesis than that of conventional melanomas. However, in a comparative genomic hybridization study comparing common blue naevi, cellular blue naevi, and atypical cellular blue naevi with melanoma associated with a blue naevus, melanomas associated with blue naevus showed chromosomal abnormalities similar to that of con-
conventional melanoma whereas cellular and atypical cellular blue naevi exhibit infrequent numerical chromosome aberrations similar in character to that identified in proliferative nodules found in congenital melanocytic naevi (1490).

Prognosis and predictive factors
Some authors have proposed that melanoma associated with blue naevus is a low-grade malignancy (1574). However, the literature review does not support this opinion. For instance, in a series of 12 cases, metastases developed in 10, and 8 died of metastatic disease (527), and in another series of 10 cases, 4 patients developed metastases and 3 of them died of disease (883). Of the 160 cases reported with follow up data, 34% of patients have died due to locally invasive or metastatic melanoma 20 months median, 41 months mean time from diagnosis (range 2–240 months). Therefore, melanoma arising in blue naevus is a highly aggressive tumour with poor prognosis similar to that of thick (>4.00 mm), AJCC stage IIB conventional melanomas (392). Indeed, the Breslow thickness for this melanoma variant typically is much greater than 4 mm with a mean tumour thickness of 10 mm (range 2.8–45 mm) (64,640,813,883,1844). Possible prognostic factors indicative of a poor outcome include the presence of congenital melanocytosis, mixed melanoma cell type (both spindle and epitheliod melanocytes), older age, high mean mitotic count (>4/40 high power field), and lymphocyte count (>100 per 20 high power field) (2332). These prognostic factors were identified in a study of primary orbital melanoma where 90% of the patients had an associated blue naevus and 47.5% had congenital melanocytosis (naevus of Ota or ocular melanocytosis). The role of sentinel lymph node dissection and postoperative adjuvant therapy remains to be determined. Sentinel lymph node dissection in the staging of melanoma associated with a blue naevus is advocated by some authors (2173) and one patient with metastatic disease to the lymph nodes was alive and without evidence of disease two years after surgery followed by therapy with interferon (640).

**Fig. 2.29** High Ki-67 labelling index in hyperchromatic spindle nuclei of the melanoma arising from blue naevus. The benign portion of the lesion (not shown) had a very low labelling index.


**Definition**
A proliferation of malignant melanocytes arising either in the epidermal component or the dermal component of a giant congenital naevus associated with risk of metastasis and death.

**ICD-O code** 8761/3

**Synonyms**
- Malignant melanoma arising in a garment naevus;
- malignant melanoma arising in a bathing trunk naevus;
- malignant melanoma arising in a giant hairy naevus.

**Epidemiology**
About 1% of all infants have some kind of a congenital pigmented skin lesion. The giant congenital naevus (GCN) is estimated to occur in around 1 per 20,000 infants. The risk of malignant transformation of a GCN has been estimated at from 5-20% but more recent studies based on statistical analyses suggest a figure of 6%. The GCN is a direct precursor of melanoma. There is a bimodal distribution to the occurrence of melanoma in GCN. Most develop in childhood before the age of 10 with a second peak of incidence in adult life.

**Macroscopy**
The lesion usually appears either as a firm nodule, or as a boggy discoloured area, usually dark brown or black in the midst of the naevus. If the lesion arises in the dermis, the tumour can sometimes only be seen on cut surface as a separate nonencapsulated nodule amidst the otherwise tan or pale tan coloured naevus in the dermis or subcutis.

**Histopathology**
Histologically, the tumours are often asymmetrical and sharply demarcated from the adjacent congenital naevus. If superficial, there is effacement of the rete ridges of the epidermis and often ulceration. The intraepidermal component usually is composed of epithelioid cells with pigmentation. Pagetoid spread is commonly noted. The tumour cells of the dermal component usually form expansile

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**Fig. 2.30** Malignant melanoma presenting as a reddish brown nodule in the midst of the congenital naevus.

**Fig. 2.31** Malignant melanoma arising from large congenital naevus. A The melanoma is clearly separate from the naevus cells that are on the left. B A protuberant nodule shows the small dark naevus cells to the left and at the base of the melanoma that is composed of nests with dyshesion.
nODULES. They exhibit fully transformed malignant characteristics with very irregular chromatin patterns and prominent nucleoli. There is variable pigmentation. Both single cell and zonal necrosis may be observed. The melanoma cells as they abut or infiltrate as cords into the adjacent naevus show no evidence of maturation but maintain their fully malignant characteristics. Mitoses are common and atypical forms are usually present. A lymphocytic host response is often noted. Occasionally, a desmoplastic host response may be observed as well as focal mucinosis. In our experience, the vertical growth phase dermal nodules may exhibit prominent areas of different cell types with different degrees of pigmentation (568, 703, 1197, 1928).

Histologically, the presence of a residual dermal naevic component with congenital features may be quite difficult to find, particularly, if present in the wall of a vessel. The differential diagnosis includes the proliferative nodules that also arise in large congenital naevi.

Somatic genetics
Comparative genomic hybridization shows that melanomas arising in congenital naevi show similar chromosomal aberrations as melanoma arising independently (175). By contrast, the proliferative nodules arising in early life do not show chromosomal aberration supporting the view that they are benign (175).

Childhood melanoma

Definition
Melanomas developing in individuals prior to the onset of puberty are childhood melanomas and thereafter they are designated as melanomas in adolescents with the age limitation of 18 to 20 years. Childhood melanomas can be further subcategorized as 1) congenital melanoma (onset in utero to birth), 2) infantile melanoma (birth to one-year of age), and 3) childhood melanoma (one year to onset of puberty).

Epidemiology
The incidence of melanoma is exceptionally rare in prepubertal individuals (estimated incidence approximately 0.4% among all melanomas) (269A, 1487A) and uncommon under the age of 20 years (incidence approximately 2%) (123A). The incidence of melanoma has doubled in patients aged 15 to 19 years over the past decade but has remained unchanged in younger individuals (204A, 1037A). Less than 80 well documented cases of melanoma in children younger than 10 years have been recorded in the literature over a period of 30 years. As in adults, childhood melanomas have a predilection for Caucasians. Individuals with congenital naevi especially large varieties, atypical naevi, family history of melanoma, xeroderma pigmentosum, and immunosuppression are at increased risk for childhood melanoma.

Localization
Melanomas developing in patients up to 16 years of age most commonly involve the trunk (50%), followed by the lower extremities (20%), head and neck (15%), and upper limbs (15%).

Clinical features
Melanomas in individuals under the age of 20, particularly in adolescents, show fairly similar clinical features as compared to melanomas in adults (123A, 1916A). However melanomas in prepubertal individuals are so rare that they are usually unsuspected. Features suggesting melanoma in a pigmented lesion such as a congenital naevus are rapid increase in size, bleeding, development of a palpable nodule (e.g., in a giant congenital naevus), colour change of a nodular lesion, surface changes such as ulceration, and loss of clearly defined margins. Recognition of melanoma appearing de novo requires a high index of clinical suspicion, especially for amelanotic lesions. Utilizing the
conventional ABCDE criteria (Asymmetry, ill-defined Borders, irregular Colour, and large Diameter, Elevation) the clinical detection of melanoma in adults, all such suspicious lesions in children should be evaluated for biopsy and histopathological examination. Melanoma in children also may be associated with pain or pruritus (155,417A,530A,1037A,1619A,1859A,1930A,1990A,2003A,2089,2232).

Histopathology
The same histopathological criteria should be utilized for diagnosis as have been developed for adult melanomas (155,159A,417A,1990A,2232). However, clinical information must be strongly considered, particularly age, since cutaneous melanoma is almost nonexistent under the age of two years and especially in the neonatal period. The important stimulants of melanoma must be excluded: 1) atypical nodular proliferations developing in congenital naevi in infants and young children and 2) Spitz naevi.

Great attention should be given to avoiding over diagnosis melanoma and at the same time to the under recognition of atypical and borderline lesions that require adequate surgery and follow-up for disease recrudescence. Lesions not clearly meeting sufficient criteria for melanoma should be designated as biologically benign. Examining atypical tumors with reference to karyotype, expression of cell-surface antigens, growth in soft agar, chromosomal aberrations, and other parameters has shown that they have the properties of an immature proliferative but benign tumor (159A,175,1496A). Variants of melanocytic proliferation and are features commonly observed in naevi developing in children, particularly in glabrous skin. These changes must not be overinterpreted unless architectural disorder is prominent and cytological abnormalities are present throughout the breadth of the lesion.

Virtually all atypical nodular melanocytic proliferations developing in congenital naevi are biologically benign. Examination of these atypical tumors with reference to karyotype, expression of cell-surface antigens, growth in soft agar, chromosomal aberrations, and other parameters has shown that they have the properties of an immature proliferative but benign tumor (71A,175,1496A).

Fig. 2.33 Small-cell melanoma from the scalp of a prepubertal individual. A The lesion resembles a conventional melanocytic naevus at scanning magnification. B High magnification shows a highly cellular dermal component without maturation. There is a monomorphous population of small round melanocytes with scant cytoplasm resembling the neoplastic cells in lymphoma or neuroendocrine carcinoma. The nuclei are pleomorphic.

Small-cell melanomas
Small-cell melanomas are comprised of monomorphous small cells, reminiscent of small round cell malignancies such as lymphoma, or a melanocytic naevus (155,159A,2232). These cells are often arranged in sheets or in organoid configurations. The melanocytes contain basophilic round nuclei and condensed chromatin. The high cellular density, lack of maturation, and often prominent mitotic rate are features suggesting melanoma. In children, small cell melanomas may appear de novo or may develop in a congenital naevus. Such melanomas with small-cell phenotypes have often been localized to the scalp, shown striking Breslow thicknesses, and fatal outcome in most patients (159A).

Melanomas simulating Spitz naevus
On occasion melanomas in both children and adults may exhibit features strongly suggesting a Spitz naevus. These features include both architectural and cytological attributes such as epidermal hyperplasia, wedge-shaped configuration, epidermal clefing about intraepidermal nests, large epithelioid cells and spindle cells arranged in fascicles, etc. (155,159A,2232).

In addition to conventional melanomas and typical Spitz naevi, there is also an intermediate group of Spitz-like lesions that demonstrate not only some features of Spitz naevi but also varying degrees of atypicality.

Differential diagnosis
Childhood melanomas must be distinguished from congenital and other naevi exhibiting pagetoid melanocytosis, lentiginous melanocytic proliferation, atypical nodular melanocytic proliferation, and from Spitz naevi. Conventional criteria such as age, clinical presentation, size, asymmetry, circumscription, degree of cellular density, maturation, degree of cytological atypia, and mitotic rate should facilitate this discrimination in most cases.

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Various authors have proposed criteria for distinguishing Spitz naevi from melanomas. Criteria favoring melanoma include asymmetry, ulceration, deep extension (particularly subcutaneous fat), large size (>1 cm), prominent cellular density, lack of maturation, deep mitoses (i.e., more than 3 mitoses in the lower third), high mitotic rate (i.e., >4 to 6/mm²), abnormal mitoses, and marked nuclear atypia.
**Naevoid melanoma**

**Definition**
Naevoid melanoma is a subtype of malignant melanoma of the skin that is distinctive in that the primary lesion mimics many of the architectural features of a common compound or intradermal naevus when composed of small melanoma cells, or with Spitz naevus when composed of medium-sized to large melanoma cells. These lesions are defined not as atypical naevi but as melanomas because they involve the dermis and have the potential for metastasis.

**ICD-O code**
8720/3

**Synonym**
The term minimal deviation melanoma has been used for some examples.

**Epidemiology**
Naevoid melanoma is uncommon, being estimated to be approximately 1–2% or less of melanomas (2096,2255). Due to the low incidence, the small size of series of studies of these tumours, and the slightly different definitions of the lesion, the demographic profiles are not well-established. Naevoid melanomas can occur at any age but often are in young to middle-aged adults. Both men and women are affected, but there is a slight female predominance, perhaps due to early detection in women. In combining data from three similar studies with a total of 65 patients, the distribution of lesions was mostly on the trunk and proximal extremities, specifically on the leg (38.5%), trunk (26.1%), arm (18.5%), head (12.3%), and neck (4.6%) (261, 262,1563,2092,2596).

**Clinical features**
The lesions are generally small papular, nodular, or verrucous, with tan to dark brown colour. The colour may be uniform or irregular. The borders of the lesion are sharp and not very irregular. The lesions often are approximately 5-10 mm in diameter (568). Clinically apparent inflammation is uncommon. The patient may report that there was a pre-existing macular pigmentation, which became a papule. The lesions are soft and non-tender. They are usually solitary lesions that often are removed because of recent growth or for cosmetic purposes.

**Etiology**
Unknown. The tumour may arise in clinically normal skin, or in a pre-existing naevus that maintains a naevus pattern of differentiation, or in a lentigo.

**Histopathology**
The microscopic features of naevoid melanoma are at present restricted by an arbitrary definition to lesions that do not have much intraepidermal spread of tumour cells (pagetoid upward migration) and have a relatively symmetrical profile at low magnification. There is sharp lateral demarcation of the lesion. Usually there are areas of sheet-like confluent melanocytic proliferation in the dermis. Some lesions have only large nests of cells in the dermis, often larger in the deep portion of the lesion when compared to the upper portion. Mitotic

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**Fig. 2.34** Naevoid melanoma. **A** Naevoid melanoma, papular lesion. (A) At low magnification, note the lack of maturation and the lack of good naevus formation in the dermis. **B** Naevoid melanoma, papular lesion. (B) At intermediate magnification, many of the cells are hyperchromatic and atypical. **C** Naevoid melanoma, papular lesion. Perivascular infiltration is at the base of the lesion.
figures can be found in the dermis in most lesions and often multiple mitoses are noted. However, small lesions may have very few mitoses. Naevoid melanomas can occupy a portion of a pre-existing intradermal or compound naevus. The melanomas have a relatively uniform population of small cells with hyperchromatic angulated nuclei or a population of medium-sized to large melanoma cells with more open nuclear chromatin and pale cytoplasm. Inflammatory reaction usually is slight and may be absent. The lesions often are dome-shaped, polypoid, or verrucous in profile (261,1562,2092,2543,2596).

Immunoprofile and other special stains
HMB-45 reactivity is variable and may be negative or positive (265,1562,1563). When positive, aberrant patterns of reactivity are common. HMB-45 reactivity may be uniform throughout the dermal portion of the lesion even though there is no junctional component. This reactivity pattern can also be found in blue naevus, some Spitz naevi, and in so-called deep penetrating naevi, and combined naevi (1563,2198). HMB-45 antibody reacts with the premelanosomal glycoprotein, gp100, and indicates an immature status of the cell with regard to melanin production. A103 antibody, which binds to the antigen Melan-A, reacts with the melanocytic cells throughout the lesion (265).

The reactivity of the tumour cells with the antibody MIB-1 to detect the protein Ki-67 in cycling cells is positive in both the upper and lower portions of the tumour. In some lesions, the reactivity is slight but greater in the deep portion than in the superficial portion of the lesion. Under controlled conditions, antibodies to detect proliferating cell nuclear antigen (PCNA) have been used to grade melanomas (1160,1934). In specimens with varied fixation conditions, PCNA has not been found to be reliable because it is sensitive to underfixation and to overfixation in formalin (1563). Silver staining of nucleolar organizing regions (AgNORs) in 10 small cell melanomas showed an average number of 5.83 (SD +/- 1.69) AgNORs per nucleus. This provided some separation from benign small dermal naevus cells, which had an average of 2.71 (SD +/- 0.50) AgNORs per nucleus. The comparison mean number in 10 superficial spreading melanomas was 8.49 (SD +/- 1.58) AgNORs per nucleus (1316).

Histogenesis
Naevoid melanomas may arise from the dermal component of small compound or intradermal naevi or from the junctional component of melanocytes in normal skin, or a pre-existing small naevus or lentigo. It is possible that some naevoid melanomas represent early nodular melanomas lacking an evident junctional component.

Prognosis and predictive factors
Predictive features of naevoid melanoma prognosis are tumour thickness, mitotic rate, and large cell type. From 3,500 melanomas, Schmoeckel et al. (2092) selected naevoid melanomas with at least 5 years of follow-up unless there was earlier metastasis. Thirty-three cases were selected: 18 were disease free for at least 5 years. Fifteen had developed metastases. Eight had died of disseminated melanoma. The "most
important criterion was tumour thickness" (but mitoses also seem important {1160}):
McNutt et al. {1562} studied 16 naevoid melanomas and observed that 2 died of melanoma (both large cell type), and one was alive with metastases (10 years, small cell type). Thirteen had wide excisions with no evidence of residual disease or were lost to follow-up.
Zembowicz et al. {2596} selected 20 cases of naevoid melanomas from their files. Three had died and 6 had metastases. There was a three-year follow-up on 8 cases, with a mean follow-up period of 2 years. They conclude: “Naevoid melanoma, as currently defined in the literature and in the present study, seems to have a prognosis similar to that of classical melanoma.”
Wong et al. {2543} studied 7 cases of naevoid melanoma (two dome-shaped and five verrucous types) and found local recurrences in 3 and regional metastasis in one patient after 2 years, with a follow-up of 5 months to 5 years.
Lohmann et al. {1444} studied 10 patients with diagnostically controversial lesions who underwent sentinel node biopsy. The differential diagnosis was between Spitz naevus and melanoma. In 5 of the 10 patients, there were sentinel node deposits of tumour in the parenchyma. All patients were alive and free of disease on follow-up of 10 to 54 months.

Variants and differential diagnosis

Minimal deviation melanoma

In the writings of Dr Richard Reed et al. {1911}, this category was analogous to the minimal deviation hepatomas of experimental liver carcinogenesis, which were thought to deviate from the normal cells by only a single enzyme defect, and greatly resembled normal hepatocytes. Initially the minimal-deviation melanomas were characterized as having small cells, without much cytologic atypia, but they all had the architectural patterns of other melanomas. As this concept evolved, minimal deviation melanomas were divided into the following types: blue naevus type, Spitz naevus type, halo naevus type, borderline melanoma, as well as the ordinary minimal deviation melanomas. This created considerable confusion, particularly since the name “minimal deviation” implies a better prognosis, which has not been a consistent finding {2255}. Naevoid melanoma as defined here was mixed into the various types of minimal deviation melanomas. This confusion is due to the use of the terms “small naevoid cell type” in small cell melanomas, just on the basis of cell size and without restrictions on the architecture of the lesion. As defined above, a diagnosis of naevoid melanoma requires both architectural and cytological mimicry of a naevus.

Recently a subtype of small-cell naevoid melanoma has been described that develops predominantly in elderly individuals with sun-damaged skin {1313}. This variant has an atypical lentiginous junctional melanocytic proliferation with a nested pattern that may be mistaken for a junctional naevus. This variant has a male predominance and the melanomas occur predominantly on the trunk. The epidemiology suggests that these junctional lesions may be precursors of lentigo maligna or superficial spreading melanoma.
melanoma in situ. This type of lesion needs further studies as to whether it represents a melanoma sui generis or a lesion with a high propensity to develop further mutations leading to melanoma. It does not fit into the current restricted definition of naevoid melanoma since it has a prominent junctional component and does not involve the dermis in the early stages.

Deep penetrating naevus
This type of naevus has a plexiform growth pattern in the dermis, and despite its name “deep penetrating” most of the lesions are restricted to the upper and middle reticular dermis, giving rise to the concept of the “superficial form of deep penetrating naevus” [2127]. The naevus cells form cords in the dermis composed of large spindled and epithelioid cells resembling a combination of the cells in a blue naevus with cells in a Spitz naevus. Mitotic figures are very rare and are not atypical. They do not have much of an epidermal component unless the deep penetrating naevus component is part of a combined naevus. They must be distinguished from naevoid melanoma, large cell type, which has mitoses in the dermis. However, some lesions given a diagnosis of deep penetrating naevus component have metastasized and may represent examples of naevoid melanomas.

Spitzoid melanoma
This designation is used primarily for melanomas that mimic a Spitz naevus. The presence of a significant junctional component and prominent pagetoid upward migration of large atypical melanocytes distinguish this tumour from a naevoid melanoma. If the Spitzoid melanoma is almost entirely intradermal, it is a variant that would fit into the definition of naevoid melanoma, large cell type.

Metastasizing Spitz naevus
A small number of lesions given the initial diagnosis of Spitz naevi have led to metastases and even the death of patients. Some cases have had only a single lymph node metastasis removed without further evidence of disease on short-term follow-up. The cases with only a single nodal metastasis have been called metastasizing Spitz naevi. Some of these lesions fit the restricted definition of naevoid melanomas if they do not have a significant junctional component. Anecdotal reports indicate that some cases classified as metastasizing Spitz naevus by one institution go to another institution years later with widespread metastases leading to death. The criteria to distinguish between Spitzoid melanoma, melanoma arising in a Spitz naevus, Spitz variant of naevoid melanoma, and metastasizing Spitz naevus are controversial and require further investigation. Examination of sentinel lymph nodes in controversial cases of Spitzoid tumours has found a significant number of nodal implants of tumour (1444).

Proliferative nodules in a congenital naevus
Benign proliferative nodules may arise in the dermis in congenital naevi in some very young patients and may be multiple. Distinction from naevoid melanoma may be difficult since mitotic figures are present in the dermal nodules of naevus cells. Features of benign proliferative nodules that have been emphasized are multiplicity of nodules of similar sizes and appearances, and a gradual blending of the cells of the nodule with the surrounding background congenital naevus cells at the periphery of the nodules. Sharp demarcation of the proliferative nodules is more common in naevoid melanomas arising in the dermal component of a congenital naevus (568).

Melanoma arising in the dermal component of a large or “giant” congenital naevus
In studies of melanomas arising in giant congenital naevi, many arose from the dermal component [254,1912,1928]. A significant proportion of such melanomas are composed of small, hyperchromatic atypical cells and were interpreted to be similar to melanoblasts, leading to diagnosis of melanoblastoma. These lesions were highly malignant. They are a variant that fits the current definition of naevoid melanoma since they lack an epidermal component and are composed of small epithelioid cells.

Early nodular melanoma
It is most likely that some naevoid melanomas are an early stage in the evolution of nodular melanomas.

Desmoplastic/neurotropic melanoma
Although some of these lesions could fit into the definition of naevoid melanoma, it is conventional to separate them as a distinct entity. Desmoplastic melanomas generally have spindle-shaped cells and naevoid melanomas, as defined here, generally have more epithelioid cells. Both tumours can present as predominantly dermal lesions. Desmoplastic melanomas can resemble desmoplastic naevi, especially hypopigmented blue naevi. Desmoplastic and neurotropic melanomas are best separated from naevoid melanomas since they can be recognized as a distinct group of tumours that has been characterized sufficiently for diagnosis.

Metastatic melanoma
The histologic features of naevoid melanoma can be exactly reproduced in satellite metastatic papules and nodules of melanoma in the skin. The lack of an intraepidermal component, confluent growth patterns, sharp circumscription, symmetry, and dermal mitotic figures can all be found in metastatic melanoma. A diagnosis of naevoid melanoma should be made with great caution in an individual with a known history of melanoma. Misdiagnosis of primary naevoid melanoma as metastatic melanoma can lead to the clinical impression of a metastatic melanoma for which a primary lesion is never found. On the other hand, individuals given a diagnosis of naevoid melanoma, who subsequently rapidly develop extensive metastases, may actually represent patients with a metastatic lesion that resembled a primary naevoid melanoma. Multiplicity of lesions resembling naevoid melanomas simultaneously in the same patient points toward metastatic disease. However multiple naevoid melanomas have been reported in an immunodeficient patient (1804).
Persistent melanoma and local metastasis of melanoma

Definition
Persistent melanoma is defined as the persistent growth of residual, incompletely excised primary malignant melanoma, of either the epidermal or the invasive component, or both. It represents one form of “local recurrence” of melanoma, the other being local metastasis (30,1001).

Synonym
Local recurrence of melanoma.

Epidemiology
The epidemiological characteristics are those of the original primary melanoma.

Etiology
The etiological factors are those of the primary melanoma.

Localization
Persistent melanoma may follow removal of melanoma from any site of the body although it seems more common on the head and neck, probably due to the higher incidence of poorly defined variants of melanoma in this site. These include lentigo maligna, in particular the amelanotic variant, and desmoplastic melanoma which is particularly susceptible to incomplete excision because of its poorly defined borders.

Clinical features
The most common clinical presentation is the persistence or recurrence of a flat,

Table 2.08
Histological features of persistent melanoma and local metastases of melanoma.

<table>
<thead>
<tr>
<th>Persistent melanoma</th>
<th>Metastatic melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal component: Usually present, with or without a dermal component.</td>
<td>A. Absent in most cases.</td>
</tr>
<tr>
<td>Dermal growth pattern: The full range of patterns associated with primary melanoma.</td>
<td>B. Epidermotropism uncommonly. The dermal component usually extends beyond a zone of epidermotropism when present. Sometimes the epidermopropic component is more extensive, simulating primary melanoma (998).</td>
</tr>
<tr>
<td>Inflammation: Lymphocytic inflammation usually present.</td>
<td>Absent or sparse.</td>
</tr>
<tr>
<td>Vascular invasion: Sometimes present.</td>
<td>Present in many cases.</td>
</tr>
<tr>
<td>Mitotic rate: Variable</td>
<td>High (usually &gt; than 6/mm²)</td>
</tr>
<tr>
<td>Cell type: The full range of cell types seen in primary melanoma, frequently including a mixture of cell types.</td>
<td>Usually monomorphic atypical melanocytic population of epithelioid, spindle or small (naevoid) cells.</td>
</tr>
<tr>
<td>Associated naevus: Commonly present.</td>
<td>Rare (coincidental).</td>
</tr>
<tr>
<td>Necrosis: Uncommon</td>
<td>Often present in the centres of the nodules.</td>
</tr>
<tr>
<td>Epidermal collarette: Uncommon</td>
<td>Usually present, when nodules of metastatic melanoma are in the superficial dermis.</td>
</tr>
<tr>
<td>Fibrosis: Frequently present in zones of regression and in desmoplasia.</td>
<td>Little or no reactive fibrosis in the stroma of the tumour.</td>
</tr>
<tr>
<td>Scarring: Present in the dermis and often also in the subcutis.</td>
<td>Present when the metastasis occurs at the primary excision site.</td>
</tr>
</tbody>
</table>

NOTE: 1. In cases of persistent melanoma, histological review of the primary excision confirms the presence of in-situ or invasive melanoma (or both) at a margin of excision. 2. The microscopic features of metastatic melanoma involving the scar of the primary excision are the same as those of metastatic melanoma at a site distant from the scar, with the additional feature of the scar at the site of the completely excised primary melanoma (2573).
variably pigmented patch adjacent to or surrounding the scar of the primary excision site. In some cases there may also be nodule formation when there is persistent dermal invasion, especially of desmoplastic melanoma.

**Macroscopy**
The lesion frequently is a variably pigmented, often pale macule with poorly defined borders. In many cases of persistent desmoplastic melanoma there is no abnormal pigmentation in the epidermis overlying a firm nodule.

**Histopathology**
In the uncommon event of incomplete excision of both the epidermal and invasive components of one of the common forms of cutaneous melanoma, the histologic appearances are those of the original tumour, frequently with pagetoid infiltration of the epidermis overlying invasive atypical epithelioid melanocytes, usually with little or no pigmentation, forming an expansile growth pattern adjacent to a zone of scarring. More commonly, the persistent lesion consists of in-situ melanoma with or without focal dermal invasion. Persistence of incompletely excised desmoplastic melanoma may present only sparse, subtle infiltration of a sclerotic nodule in the dermis and/or subcutis, containing atypical spindle cells with hyperchromatic, variably pleomorphic nuclei and sometimes only sparse mitoses, distributed singly and in strands between the collagen bundles. As in the primary tumour, a patchy lymphocytic infiltrate may provide a clue to perineural invasion. Desmoplastic melanoma may very closely simulate a surgical scar in the primary lesion and can be very poorly circumscribed (1194). However it can be distinguished by its infiltrative pattern beyond the zone usually expected to be involved with scarring following surgery. The features of persistent desmoplastic/neurotropic melanoma may be seen proximal or distal to the scar at the primary excision site, along the line of nerves.

In assessing locally recurrent melanoma it should always be remembered that melanoma metastases may be epidermotropic and simulate primary melanoma (998).

**Differential diagnosis**
Rarely, pigmentation of the epidermis or growth of a nodule at the site of previous excision of melanoma may be due to the coincidental growth of an entirely new and distinct tumour such as dermatofibroma or pigmented basal cell carcinoma. The most important differential diagnosis, however, lies between true persistence of incompletely excised primary melanoma and the other form of “local recurrence” due to metastatic melanoma. Metastatic melanoma in or adjacent to the primary excision scar usually presents as a rapidly growing papule or nodule without pigmentation of the overlying dermis, sometimes associated with...
multiple similar, rapidly growing lesions separate from the primary excision site. Histologically, metastases involving the scar present exactly the same features as cutaneous metastases at a distance from the scar (2573).

**Histogenesis**
Persistent melanoma occurs because a primary melanoma was incompletely excised. The histogenesis, therefore, is essentially that of the original melanoma.

**Somatic genetics**
The genetic factors are those that apply to the original melanoma.

**Prognosis and predictive factors**
The prognosis for persistent melanoma is assessed in the same manner as for the original tumour, tumour thickness still being the most important single factor, unlike local recurrence due to metastasis which is a manifestation of systemic metastasis and portends a poor prognosis.

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*Fig. 2.40* Metastatic melanoma. A In this epidermotropic metastatic melanoma, a papule has formed largely due to the irregular epidermal hyperplasia. B On the left side of the lesion, one can see sharp circumscription, contributing to resemblance to a Spitz naevus. C Metastatic melanoma simulating blue naevus. D Irregular nests of melanoma cells are visible at the base of the lesion in the subcutis.
Congenital melanocytic naevus

**Superficial type**

**Definition**
Congenital melanocytic naevi (CMN) of the superficial type are melanocytic proliferations present at birth. The term congenital has been also applied to lesions displaying clinical and histopathological features of congenital melanocytic naevi which may not be apparent at birth. These lesions are designated as tardive congenital melanocytic naevi.

**ICD-O code**
8761/0

**Synonyms**
Congenital pattern-like naevus; tardive congenital naevus; congenital naevus-like naevus.

**Clinical features**
Congenital melanocytic naevi - superficial type are frequently observed. They can be found on any anatomic site and belong to the group of small congenital naevi with a diameter smaller than 1.5 cm.

On gross examination they vary from macules and papules to plaques and reveal different colours from light brown to black. The lesions are usually round or oval with a smooth or papillated surface. They may be hairy or hairless.

**Histopathology**
In the superficial type of CMN, dense diffuse infiltrates of small monomorphous melanocytes are found in the upper part of the dermis and the mid-portion of the reticular dermis. The melanocytes are frequently arranged in a band-like pattern and are disposed in single files between collagen bundles (“splaying of melanocytes”).

An important criterion for diagnosis is the presence of melanocytes along epithelial structures of adnexa and their angiocentric distribution. They may be found within sebaceous glands, vessels, nerves and in smooth muscles {1168,1531}. In the compound type of a congenital naevus – superficial type, nests of melanocytes are present in the epidermis, mostly at the dermo-epidermal junction. Melanomas are very rare in newborn and young infants (see chapter on childhood melanoma). Congenital melanocytic naevi, biopsied shortly after birth or in the first years of life can display atypical intraepidermal changes (pagetoid melanocytes arranged as solitary units and nests; single cells present in the upper layers of the epidermis) similar to those of melanoma in situ {1514}. This finding is more commonly found in giant congenital naevi than in small ones.

The clues for diagnosis of this unusual change in a benign naevus are found in the dermis where the large, pale melanocytes merge with smaller ones that have the characteristic features of a congenital melanocytic naevus.

**Somatic genetics**
Like the majority of melanocytic naevi except Spitz and blue naevi, congenital melanocytic naevi have frequent BRAF mutations and show no chromosomal aberrations {173,1850}.

**Prognosis and predictive factors**
Recent studies revealed in a significant number of malignant melanomas an association with melanocytic naevi with a congenital histopathologic pattern {159,1245}. However, the pathogenetic role of small congenital melanocytic naevi as precursor lesions of melanoma is controversial {1508, 2323}. Clinical follow-up of 3922 patients with small CMN found no significant risk of melanoma development {205}.

**Proliferative nodules in congenital melanocytic naevi**

**Definition**
Proliferative nodules in congenital melanocytic naevi are defined as atypical melanocytic proliferations which manifest predominantly in the neonatal period within a pre-existing large (deep) congenital melanocytic naevus.

**ICD-O code**
8762/1

**Synonyms**
Atypical proliferative nodules in giant...
congenital naevi; dermal variant of minimal deviation melanoma in a giant congenital naevus (1907), dermal melanocytic tumour of uncertain potential in a giant congenital naevus.

Clinical features
There is usually a dark brown to black plaque or nodule above a giant congenital melanocytic naevus. The lesions may become lighter and show regression after years. Occasionally a palpable mass can be found deeply in the skin. These nodular proliferations in congenital melanocytic naevi behave in a benign fashion.

Histopathology
The background congenital melanocytic naevus reveals the characteristic features of a congenital melanocytic naevus of the deep type. A dense diffuse infiltrate of small melanocytes involving the entire dermis and often extending into the septa of the subcutaneous fat can be observed.

The "proliferative" nodule, which is usually found in the upper and mid dermis consists of roundish epithelioid or spindled melanocytes. The cells are large and appear to blend with the surrounding smaller melanocytes (naevus cells). Atypical nuclei and mitotic figures can be observed.

Differential diagnosis
Proliferative nodules in congenital melanocytic naevi can be misinterpreted as a melanoma that developed in the intradermal component of a congenital naevus (see Melanoma arising in giant congenital naevi) (1009).

Somatic genetics
In a study of proliferative nodules using comparative genomic hybridization seven out of nine cases showed chromosomal aberrations (175). Six of the seven cases with aberrations (86%) showed numerical aberrations of whole chromosomes exclusively. This pattern differs significantly from the findings in melanomas arising in congenital naevi or melanoma in general in which the majority (96%) have aberrations involving only partial chromosomes (173). Loss of chromosome 7 was seen in three of the nine proliferative nodules. Loss of chromosome 7 was not observed in 132 melanomas that were not associated with giant congenital naevi (173). However, one melanoma arising in a congenital naevus in an eight-year-old boy showed a similar loss of chromosome 7.
**Common blue naevus**

**Definition**
Common blue naevus (BN) is a benign, usually intradermal melanocytic lesion characterized by pigmented dendritic spindle-shaped melanocytes and, more rarely, epithelioid melanocytes. The melanocytes are usually separated by thickened collagen bundles.

**ICD-O code** 8780/0

**Epidemiology**
BN is relatively frequent, has predilection for females and presents mainly in young adults between the second and fourth decades. Although most tumours are acquired, congenital examples have been documented (1872). Familial cases may be seen and usually present with multiple lesions (258,1292).

**Localization**
The anatomical distribution is wide but most lesions occur on the distal upper limbs (particularly the dorsum of the hand), followed by the lower limbs, scalp, face and buttocks. Lesions have also been documented in the vagina (1002,2356), cervix (2393), prostate (1414), oral cavity (mainly the hard palate) (327,328) and the capsule of lymph nodes without a primary cutaneous lesion (695,858,1497).

**Clinical features**
The most common presentation consists of a single asymptomatic, relatively well-circumscribed, dome-shaped blue or blue-black papule less than 1 cm in diameter. The characteristic blue colour is produced by the Tyndall effect. Tumours may rarely present as a plaque (1025,2494). Eruptive lesions have rarely been documented. Exceptional clinical presentations include a speckled variant (1044), hypopigmented lesions (278), an example with satellite lesions (1195) and a case with widespread lesions. Localized hypertrichosis has been described in a single case (57).

**Histopathology**
BN and cellular blue naevus show a wide histological spectrum, frequently overlapping with other melanocytic lesions including deep penetrating naevus and pigmented Spitz naevus (1637). BN is typically located in the reticular dermis and only exceptionally extends into the papillary dermis or subcutis. The epidermis appears unremarkable, except in the rare so-called compound blue naevus, in which dendritic junctional melanocytes are identified (733,1190). Low power examination reveals a generally symmetric but often ill-defined tumour of variable cellularity. Concentration around adnexa without adnexal destruction is typical. Poorly cellular lesions often display prominent sclerotic stroma making the diagnosis difficult. Lesions with very poor pigmentation are rarely encountered (234,402). Tumour cells are bland and spindle-shaped or dendritic and usually contain abundant cytoplasmic coarse melanin pigment. Nuclei are small, and an inconspicuous basophilic nucleolus is sometimes present. Numerous melanophages are a relatively constant feature in the vicinity of tumour cells. Extension of tumour cells into nerves and, less frequently, blood vessel walls, may be found. Mitotic figures are exceptional. Rarely, a blue naevus may coexist with a trichoepithelioma (48). In some instances, metastatic melanoma may mimic common blue naevus (354). Blue naevus may co-exists with other types of naevus (see combined naevus).

**Immunoprofile**
Tumour cells are usually diffusely positive for melanocytic markers including S-100, HMB45, melan A and microphthalmia transcription factor (MITF-1). Unlike the case in most other benign melanocytic naevi and in melanomas, HMB45 strongly stains the entire lesion in blue naevi.

**Somatic genetics**
Mutations in the BRAF gene appear to be rare in BN. Chromosomal aberrations are uncommon (1490).
Prognosis and predictive factors

BN is benign, and malignant transformation is exceptional (883) (see chapter Melanoma arising from blue naevus). Simple excision is curative and local recurrence is very rare (973).

Mongolian spot

Definition
Mongolian spot (MS) is a form of dermal melanocytosis presenting on the lower back and characterized by scattered pigmented dendritic melanocytes in the reticular dermis.

Epidemiology
MS presents at birth and has marked predilection for Black and Oriental patients with the same sex incidence (1260,1261). The incidence in Caucasian children is approximately 9.5% (543).

Localization
Most lesions occur on the lower posterior trunk with predilection for the sacro-gluteal region. Lesions identical to MS and naevus of Ito or naevus of Ota may present rarely in other anatomical sites.

Clinical features
Lesions are usually large, macular, ill defined and have a blue or blue-grey colour. A speckled appearance is seen rarely. There is no tendency for spontaneous regression. Bilateral involvement has been documented rarely (1026). Coexistence between NI and NO is a rare occurrence (615,1026). Glaucoma is a rare complication of NO (1434).

Histopathology
The histology of NI and NO is indistinguishable. The epidermis appears unremarkable but may show increased melanin in basal cells and a mild increase in the number of basal melanocytes. In the superficial and mid-dermis there are scattered dendritic or spindle-shaped, often bipolar deeply pigmented melanocytes. Melanophages are rare.

Naevus of Ito and Naevus of Ota

Definition
Naevus of Ito (NI) and naevus of Ota (NO) are dermal melanocytoses with identical histological features, which differ in their characteristic clinical presentation. NI typically presents in the shoulder region, following the distribution of the lateral brachial and posterior supraclavicular nerves. NO involves the skin and mucosal surfaces (including the conjunctiva), following the distribution of the ophthalmic and maxillary branches of the trigeminal nerve.

Synonyms
Naevus Ota: Oculodermal melanocytosis, Naevus fuscoceruleus ophthalmomaxillaris.

Epidemiology
Both NI and NO are relatively rare, affect mainly patients of Oriental or African origin and have some predilection for females (1027,1307,1626,2243). Presentation is mainly at birth (up to 50%) or during childhood and adolescence. Adult onset is very rare (447).

Localization
NI typically involves the supraclavicular, deltoid and less commonly, the scapular area. NO usually involves the sclera, conjunctiva, and skin around the eye and zygomatic and temporal areas. Rarely the nasal and oral mucosa, optic tract and the leptomeninges are involved. Lesions identical to naevus of Ito or naevus of Ota may present rarely in other anatomical sites. A limited form resembling naevus of Ota presenting in the zygomatic area is called naevus of Sun.

Clinical features
Lesions are usually large, macular, ill defined and have a blue or blue-grey colour. A speckled appearance is seen rarely. There is no tendency for spontaneous regression. Bilateral involvement has been documented rarely (1026). Coexistence between NI and NO is a rare occurrence (615,1026). Glaucoma is a rare complication of NO (1434).

Histopathology
The histology of NI and NO is indistinguishable. The epidermis appears unremarkable but may show increased melanin in basal cells and a mild increase in the number of basal melanocytes. In the superficial and mid-dermis there are scattered dendritic or spindle-shaped, often bipolar deeply pigmented melanocytes. Melanophages are rare.

Prognosis and predictive factors
Malignant transformation is exceptional and more common in NO (1783,2194,2345,2414). In the latter setting it may occur in the skin, eye or meninges.

Cellular blue naevus

Definition
Cellular blue naevus (CBN) is an acquired dermal/subcutaneous pigmented tumour with prominent cellularity and an expansile growth pattern.

ICD-O code 8790/0
Epidemiology
CBN tends to present between the second and fourth decades of life with female predilection, and it is more common in Caucasians. Congenital cases are exceptional (1095).

Localization
The anatomical distribution is wide, but CBN have predilection for the buttocks and sacral region (50% of cases), followed by the scalp, face, distal limbs and other sites on the trunk (1957,2336). Lesions may also rarely occur on the eyes, cervix, vagina, breast and spermatic cord (266,1957,2336). Aggregates of tumour cells have been reported in the capsules of regional lymph nodes draining an area where an otherwise typical benign cellular blue naevus is present (287,1957,2261,2336). This phenomenon is regarded as a benign occurrence rather than an ominous finding.

Clinical features
Tumours are usually large, varying from 1 to several centimetres, and the colour varies from light blue-brown to dark blue. Lesions are asymptomatic and grow very slowly, presenting as a non-ulcerated firm nodule (1957,2336). Exceptional cases present as a large plaque (358). Rare tumours arising in the scalp have been described with invasion of the underlying bone (1596) and even the brain (854). The epithelioid variant of blue naevus is very rare and has mainly been described in patients with Carney complex who usually present with multiple lesions (396,399). Sporadic lesions are usually solitary and may occur in genital skin (1117,1646,1736).

Macroscopy
The cut surface of a CBN characteristically shows a dark brown to black, well-defined dermal and subcutaneous tumour. In some cases there are areas of haemorrhage and cystic degeneration.

Histopathology
Low-power examination reveals a fairly characteristic picture with a dumbbell-shaped multinodular tumour occupying the reticular dermis and often extending into subcutaneous tissue. A junctional component is not usually found. Areas of pigmentation alternate with poorly pigmented areas and, in a minority of cases, pigment is very scanty (2595). Cellular areas tend to be more prominent towards the centre of the tumour, and the cellularity may be most marked where the neoplasm protrudes into the subcutis. The cellular areas may alternate with sclerotic or hypocellular areas. In most cases there are focal areas representing or simulating a common blue naevus. High power examination reveals bundles of oval or spindle-shaped cells with pale cytoplasm, alternating with bundles of deeply pigmented spindle-shaped cells. In addition, dendritic melanocytes and/or round, somewhat epithelioid melanosomes may be seen. Cytoplasmic melanin is coarse and granular, and nuclei are regular and vesicular, with a single small inconspicuous basophilic nucleolus. Maturation with depth is not a feature. A frequent finding however, is the focal presence of elongated slender melanocytes resembling Schwann cells, indicative of neurotization as seen in ordinary naevi. Some tumours exhibit a focal alveolar growth pattern (1597) and desmoplasia is occasionally prominent (1599). Degenerative changes including haemorrhage, cystic change and fibrosis, are seen in some cases. Focal mild or prominent myxoid oedematous change may also be a feature (1598), and balloon cell change has been documented (1806). Occasional cases display a number of unusual features including mitotic figures (1/10 HPFs), focal necrosis, and/or nuclear pleomorphism or hyperchromatism. Such cases show some overlap with the malignant variant of CBN and have been described as atypical CBN (118,2371).

The epithelioid blue naevus is composed of large round epithelioid and short spindle-shaped deeply pigmented melano-
cytes. Some examples of this variant of BN probably represent combined naevi (903).

**Immunoprofile**

Tumour cells in CBN are positive for S-100, melan-A and HMB45. In tumours with prominent desmoplasia, and in those with neurotization, staining for melan-A and HMB45 tends to be patchy. CD34 has been reported to be positive in tumour cells in a group of congenital CBN (2204).

**Genetics**

Similar to other naevi, cellular blue naevi do not show chromosomal aberrations when analysed by CGH. In a small series of atypical cellular blue naevi, three out of eight cases showed single chromosomal losses with chromosome 3p being affected in two of these cases (1490).

**Prognosis and predictive factors**

Although limited case series have characterized these lesions as benign, some cases with atypical features have resulted in recurrences or death from systemic metastasis. They may therefore be regarded as having uncertain malignant potential and treated with complete excision if possible and perhaps long term follow-up. Malignant transformation in CBN is very rare (64,883).

### Deep penetrating naevus

**Definition**

Deep penetrating naevus (DPN) is a distinctive deeply pigmented lesion showing overlapping features with blue naevus and Spitz naevus.

**Synonym**

Some cases have been described under the heading of plexiform spindle cell naevus (164).

**Epidemiology**

DPN is an acquired lesion presenting mainly between the second and third decades of life with no sex predilection (1953,2127).

**Localization**

DPN has a wide anatomical distribution with predilection for the face, upper trunk and proximal limbs (164,537,1575,1953, 2127).

**Clinical features**

The tumour presents as a solitary, well-circumscribed blue or dark brown/black dome-shaped papule or nodule usually less than 1 cm in diameter.

**Histopathology**

Low power examination typically reveals a compound wedge-shaped deeply pig-mented dermal and, very rarely, superficial subcutaneous tumour. The base of the lesion parallels the epidermis. The junctional component, which is usually present and may be subtle, consists of small round nests of ordinary naevus cells. In fact, in most cases, a superficial dermal component, representing an ordinary naevus, may be found and therefore these lesions may be regarded as combined naevi (1953). Much less commonly, focal changes mimicking a Spitz naevus or a blue naevus are found (1953, 2127). Tumour cells are arranged in nests or bundles and have a short spindle-shaped or, less commonly, round morphology. The cytoplasm contains...
abundant melanin and nuclei are vesicular with frequent intranuclear inclusions and a single small basophilic nucleolus. Hyperchromatism and variation in nuclear size may be seen, but as a rule mitotic activity is low or absent (usually not more than 1 per section). The melanocytes follow the path of adnexal structures and blood vessels and there is frequent perineural extension. Maturation is not seen. Some tumours have the cytomorphology of DPN but are superficial and lack the deep penetrating component. Similar changes are seen in a common form of combined naevus.

**Prognosis and predictive factors**
Local recurrence is exceptional, and only a single case has been reported spreading to a regional lymph node (874).

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**Fig. 2.51** Deep penetrating naevus. **A** A wedge shape and nests of cells around adnexal structures are characteristic findings. **B** The large pale cells in a deep penetrating naevus are arranged as discrete nests. **C** A thin rim of sustentacular cells is present around the edges of many nests. **D** Toward the base of the lesion nests of pale large cells are present near adnexal structures.
Combined naevus

Definition
A combined naevus or “melanocytic naevus with phenotypic heterogeneity” is a melanocytic naevus either congenital or acquired, containing two or more distinct melanocytic naevus components.

Synonyms and historical annotation
Melanocytic naevus with phenotypic heterogeneity; inverted type A naevus; naevus with focal dermal epithelioid component, and naevi with dermal nodules.

The term combined naevus was used initially to describe the combination of a conventional naevus and blue naevus (61,653,702,1402,2331). However, the spectrum of combined naevus has been subsequently extended to include components of any type of naevus (Table 2.09)(135,156,520,1610). There may be poor concordance in the interpretation of some cases, because of overlapping features and the difficulty of defining the morphological limits of blue naevi, Spitz naevi, deep penetrating naevi, plexiform pigmented spindle cell naevi, and naevi with dermal epithelioid cell components.

Epidemiology
There are no population-based data available as to the prevalence of combined naevi. However they appear to constitute less than 1% of melanocytic naevi sampled for histopathological examination (2116). These naevi occur in all age groups (3 to 83 years in a recent study) with a mean age of 30 years (2116). A slight predominance of women has been consistently reported in several studies (757,1864,1961,2116).

The developmental biology of combined naevi has not been delineated. Their genesis may be related to more than one pathway of melanocytic differentiation occurring in a single naevus. It cannot be excluded that there is focal neoplastic progression in some proportion of these lesions.

Localization
Scolyer et al. found a predilection for the trunk (chest, back, abdomen) in 35.2% of cases, the head and neck in 23.6%, upper extremities in 22.0%, lower extremities in 9.9%, and perineum and buttocks in 4.4% (2116). Naevi with a significant blue naevus component commonly involve the face, back, and shoulder (757). Naevi with prominent components of Spitz naevus often occur on the head and neck (face) or extremities as do conventional Spitz naevi (1961).

Clinical features
The gross morphological features of combined naevi are probably related to the types of and predominant cellular populations present, e.g., focal dermal pigmented components, blue naevus, Spitz naevus, etc. Most of these naevi measure less than 5 to 6 mm in greatest diameter (156,757,1864,2116), are reasonably symmetrical, are well-circumscribed papular or dome-shaped lesions, and exhibit dark brown, blue to black colouration. Thus many such naevi are often diagnosed clinically as blue naevi or melanoma because of the predominant dark colour. Some of these naevi may also demonstrate a small well-circumscribed blue or blue-black focus, e.g., often 1–3 mm in diameter, within an otherwise ordinary flesh-coloured, tan, or brown naevus (melanocytic naevi with focal dermal pigmented components) (135,156,520,757,2116). Some naevi may show irregular borders and pigment patterns also raising concern for melanoma.

Naevi with prominent Spitz components are often diagnosed as an unusual naevus, Spitz naevus, dermatofibroma, or possibly melanoma.

Histopathology
Combined naevi may potentially encompass the entire phenotypic repertoire of melanocytic naevi. By definition two or more distinct naevus components are present. Any combination of naevus components and percentage of the naevus components may occur. However 99% of combined naevi have only two components (2116). The two components are intimately admixed in 82% of cases whereas they are adjacent in the remainder. The most common pattern of combined naevus is that of a common acquired or congenital naevus in combination with discreet foci of pigmented epithelioid and/or spindle cells (which probably includes inverted type A naevus and melanocytic naevus with dermal epithelioid cell components, dermal nodules, or a component of “deep penetrating” or plexiform pigmented spindle cell naevus) (158,164,537,2126). The latter cells are often enlarged, contain abundant granular melanin, and are disposed in nests or fascicles in the superficial, superficial and deep, or deep portions of or beneath the ordinary naevus, sometimes or commonly in plexiform arrangements. The sizes of the nests or fascicles

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Table 2.09 The naevus components potentially occurring in combined naevus

<table>
<thead>
<tr>
<th>Component Type</th>
<th>Example Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common acquired naevi</td>
<td>- junctional - compound - dermal</td>
</tr>
<tr>
<td>Congenital naevi</td>
<td>- junctional - compound - dermal</td>
</tr>
<tr>
<td>Dysplastic naevi (naevi with architectural disorder and cytological atypia)</td>
<td>- junctional - compound</td>
</tr>
<tr>
<td>Spitz naevi</td>
<td>- junctional - compound - dermal - desmoplastic</td>
</tr>
<tr>
<td>Blue naevi</td>
<td>- ordinary or common - hypercellular - cellular - plaque - epithelioid</td>
</tr>
<tr>
<td>Deep penetrating naevi</td>
<td>- pigmented spindle cell naevi</td>
</tr>
<tr>
<td>Naevi with dermal epithelioid cell components</td>
<td>- clonal naevus - inverted type A naevus - naevus with dermal nodules</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

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R.L. Barnhill
may vary from being minuscule to large lobular or digitate aggregates. The nuclei are usually comparable in size to the surrounding conventional naevus cells, or may be slightly enlarged round, oval, or elongate and uniform. On occasion the nuclei may show variable often slight to moderate atypia. Melanophages are also frequently associated with these pigmented foci. This pattern of combined naevus is also probably morphologically identical to that of deep-penetrating naevus and plexiform pigmented spindle cell naevus. Another common pattern is that of an ordinary naevus and blue naevus. The ordinary naevus component may be compound or dermal, often overlies or is adjacent to the blue naevus component, and commonly has a congenital pattern. The blue naevus elements most often consist of heavily-pigmented dendritic melanocytes, melanophages, and variable fibrosis. Less commonly, the spindle cells typical of cellular blue naevus may also be present with or without dendritic cells. The component of blue naevus may extend deeply into the reticular dermis as nests or fascicles, often in a plexiform configuration. Despite the two or more components, such naevi are usually symmetric, well-circumscribed, orderly, and display little or no cellular atypia. Spitz naevi uncommonly are observed in association with ordinary naevus elements. The topographic relationships of these two components include the Spitz naevus component being adjacent to, beneath, or admixed with the common naevus elements. Such naevi also may have a desmoplastic stroma as in desmoplastic Spitz naevi. After the above relatively well-recognized forms of combined naevus, almost any combination of cell types is possible. Thus, one may encounter naevi containing various admixtures of ordinary naevus cells, dendritic melanocytes, Spitz naevus cells, and perhaps other transitional cell types. Atypical features may also be observed such as disordered patterns of melanocytes and cytological atypia of both the intraepidermal and dermal components.

**Somatic genetics**

The conventional naevus component will demonstrate frequent BRAF mutations in contrast to their absence in blue or Spitz naevus components.

**Differential diagnosis**

The differential diagnosis of combined naevus is dependent on the particular cellular populations present. The histological feature often of most concern is
Melanocytic tumours

an aberrant focus of cytologically altered/atypical cells in an otherwise ordinary naevus. Such a finding is of concern for early transformation to melanoma or, even fully-evolved melanoma. The latter histologic alteration is present most commonly in the dermis. However, the development of melanoma in the dermal component of a naevus is highly unusual. Therefore, such a diagnosis must be carefully considered and based on sufficient criteria of atypicality, mitotic activity, nodular (confluent) proliferation, and usually the lack of transition (maturation) to the surrounding naevus. Although combined naevi are heterogeneous, they are usually present in young individuals (< 30 to 40 years), measure less than 5 or 6 mm, and exhibit an overall symmetry and regular appearance. A focal aggregate of pigment-laden epithelioid/spindle cells is usually the feature of concern. Although occasional aggregates of epithelioid cells are large, many are small and well-circumscribed. Cytologic atypia is usually low-grade or insignificant compared to melanoma. The surrounding naevus which commonly is of ordinary type is generally unremarkable with reference to atypicality. An occasional mitosis may be observed in such a focus without undue concern; however, the presence of 2 or more mitoses per high power field should prompt careful inspection for melanoma (156).

Prognosis and predictive factors

Combined naevi are by definition benign. However it must be acknowledged that as with cellular blue naevi and Spitz naevi, there are unusual variants often characterized by a number of abnormal features. Such atypical lesions rarely may result in metastases and require further study as to more definitive criteria for malignancy. Thus such atypical variants prospectively are best designated as biologically indeterminate and require complete excision and close clinical monitoring.

Table 2.10

<table>
<thead>
<tr>
<th></th>
<th>Combined naevus</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetry</td>
<td>Frequent</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Size</td>
<td>&lt; 6mm often</td>
<td>&gt; 1cm often</td>
</tr>
<tr>
<td>Lateral border</td>
<td>Sharply defined</td>
<td>Poorly-defined</td>
</tr>
<tr>
<td>Focus, foci of altered cells*</td>
<td>Present, transition (maturation) to surrounding ordinary naevus</td>
<td>Variable</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>Usually absent or low-grade</td>
<td>High-grade</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>Absent or minimal (usually &lt; 2/mm²)</td>
<td>Frequent</td>
</tr>
<tr>
<td>Mononuclear cell infiltrates</td>
<td>Uncommon</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

*Focus of epithelioid/spindle cells in ordinary naevus (as also observed in inverted type A and clonal naevi)
Melanotic macules, simple lentigo and lentiginous melanocytic naevus

**Melanotic macules**

**Definition**
Melanotic macules are pigmented lesions that occur on skin, mucous membranes, and in nail units (2035). The lesions are characterized by hyperpigmentation of the epidermal/epithelial basal layer accompanied by a slight increase in number of melanocytes. There are several syndromes, which are associated with multiple melanotic macules/lentigines (Peutz-Jeghers, NAME, LAMB, LEOPARD, Carney complex (See Chapter 7).

**Synonyms**
Genital: Genital melanosis/lentiginosis; Vulvar melanotic macule; penile melanotic macule; penile lentigo.
Labial/oral: Labial/oral melanosis; labial melanotic macule; labial lentigo.
Volar: Volar melanosis.
Nail apparatus: Melanosis of the nail bed and matrix; ungual melanosis.
Skin: Reticulated black solar lentigo; “ink spot” lentigo.

**Clinical features**
**Melanotic macule of vulvar and other female genital sites**
The condition occurs usually on the vulva as a flat asymmetric macule with a diameter from less than 1–5 cm. Multiple lesions are present in >50% of the cases. The tan-brown to blue-black macules mostly involve the labia minora. But they can also occur on the labia majora, perineum, the introitus, vagina and cervix. They may be difficult to distinguish from melanoma (1400).

**Penile melanotic macule**
This lesion usually presents in adult life as a pigmented patch, uniform or variegated in colour with irregular borders, on the glans penis or on the penile shaft. Multiple macules can be observed.

**Labial melanotic macule**
The lesion occurs in about 3% of persons, mostly in women on the vermilion border of the lower lip. The lesions can be also present on the oral mucosa and on the tongue. A single or multiple (oral melanosis), brownish-black or black macules with irregular sharply demarcated borders can be observed (925).

**Variants**
**Volar melanotic macule**
Clinically a brown, tan, or grey macule (less than 5 mm in diameter) is located on palms and soles usually in Black patients.

**Ungual melanotic macule**
Pigmented bands (not thicker than 3 mm) are observed in the fingernails of young individuals (longitudinal melanonychia). The lesions are common in dark-skinned races and in the Japanese population. In Laugier-Hunziker syndrome, longitudinal melanonychia is accompanied with labial/oral melanotic macules.

**Reticulated melanotic macule**
These lesions appear on sun-exposed areas of the trunk or shoulders as a dark-brown or black reticulated macule with irregular borders. Although the lesion has been named “reticulated black solar lentigo” (277), it is different from the conventional solar lentigo (1171).

**PUVA-lentigines**
PUVA-lentigines are pigmented macules, which develop as a direct response to the effects of long-term therapy with PUVA (psoralens + UVA).

**Histopathology**
Similar histopathologic changes can be demonstrated in all types of melanotic macules. There is usually no perceptible or a slight increase in the number of melanocytes, which are situated at the dermo-epidermal junction in solitary units. The melanocytes exhibit small and monomorphous nuclei and delicate dendrites. Using Fontana-Masson silver stain, the dendrites are better visible. Atypia is not observed. The basal layer reveals prominent hyperpigmentation. Occasionally hyperplasia of the epidermis can be seen. Melanophages and a mild inflammatory infiltrate are often present in the superficial dermis.

Reticulated melanotic macules show marked hyperpigmentation of the epidermis especially at the tips of the rete ridges whereas the suprapapillary plates are spared and nearly devoid of melanin. A slightly increased number of finely dendritic melanocytes can be observed in the lower layers of the epidermis. In contrast, solar lentigo represents an evolving seborrhoeic keratosis revealing small buds or nubbins of hyperpigmented keratinocytes.

PUVA-lentigines are characterized by an increased number of melanocytes, which are concentrated mostly in pigmented rete ridges as solitary units. Some melanocytes may show atypical nuclei.

![Fig. 2.53](image-url) **Fig. 2.53** Melanotic macule on the lip. **A** Brown-black macule with irregular margins on the lower lip. **B** Pigmentation of the epithelial basal layer and melanophages in the papillary dermis.
Differential diagnosis

Early stages of melanoma in situ must be differentiated from melanotic macules. Melanoma in situ (genital / labial areas) can manifest as a sparsely cellular proliferation of melanocytes. Sometimes in a partial biopsy the only clues are nuclear hyperchromasia or irregularly shaped dendrites. In more fully developed cases, melanocytes are more regularly distributed, can become confluent and may also be situated above the junction. Lesions with more than a slight increase in melanocytes, even without atypia should be carefully evaluated, with additional sampling, over time if indicated. If the problem cannot be resolved complete excision may be appropriate.

**Simple lentigo – lentiginous melanocytic naevus**

**Definition**

Simple lentigo and lentiginous melanocytic naevus are pigmented macules representing the early stages in the development of a melanocytic naevus. In simple lentigo, melanocytes are increased in number along the basal layer; lentiginous junctional melanocytic naevus shows in addition formation of small junctional nests. In compound lentiginous melanocytic naevi, small round melanocytes are also present in the papillary dermis.

**Synonyms**

Lentigo simplex, naevus incipiens.

**Clinical features**

Small flat roundish uniform brown or black sharply circumscribed macules usually less than 6 mm in diameter, which are most frequently found on the trunk and extremities of children and adults, are observed.

**Histopathology**

Simple lentigo consists of an increased number of melanocytes disposed as solitary units in the basal layer of variably elongated and hyperpigmented rete ridges. The melanocytes have small round to oval and monomorphous nuclei. They are positioned equidistant from one another and are seen more pronounced at the tips of the rete ridges. Pigment is abundant and found throughout the epidermis including the stratum corneum. Melanophages are usually present in the papillary dermis. Giant melanosomes can be present. When one or more small nests of melanocytes (i.e. three or more melanocytes per congregation) in such a lesion is observed, it is then called lentiginous naevus (evolving junctional naevus). The histology of naevus spilus (congenital speckled lentiginous naevus) is indistinguishable from simple lentigo-lentiginous melanocytic junctional naevus.

**Prognosis and predictive factors**

Melanotic macules have been incorrectly interpreted as premalignant lesions and possible precursors of melanoma (1757A,2394A). Current evidence supports the notion that melanotic macules, irrespective of their location, should be considered benign in their clinical behaviour, since they tend to remain stable and unchanged when followed over a long period of time. Simple lentigo and lentiginous melanocytic naevus are wholly benign melanocytic proliferations which have no potential for malignant transformation.
Dysplastic naevus

Definition
Solitary or multiple naevi, variable in colour, border, and size, with preferential location on the upper trunk and extremities. Dysplastic naevi (DN) occur as sporadic lesions and in a familial setting. They may progress to malignant melanoma.

ICD-O code 8727/0

Synonyms
Atypical naevus (896) has been proposed as a synonym for clinically dysplastic naevus. Other past designations include naevus with architectural disorder (1), and melanocytic naevus with architectural disorder and cytologic atypia (1,2158). The concept of Clark naevus includes a large number of junctional and superficial compound naevi of which the dysplastic naevus is a subset.

Historical annotation
Originally, Wallace H. Clark and coworkers described patients with multiple atypical naevi for which they proposed the term “B-K mole syndrome”, using the first initial of the surname of two probands (496). The authors photographically documented two lesions that progressed over time to malignant melanoma. Therefore, the authors considered the “B-K mole” a precursor of melanoma. Soon thereafter, in 1980, Elder et al found lesions similar to those in “B-K mole” patients with non-familial cutaneous malignant melanoma (673). Subsequently, the “B-K Mole Syndrome” was renamed to “Dysplastic Naevus Syndrome”, with further sub-classification into sporadic or familial types. In 1992, a U.S. National Institutes of Health Consensus Conference recommended “naevus with architectural disorder” in order to avoid the negative connotation associated with the word “dysplasia” (1). However, this term has failed to gain wide acceptance (2153). In a recent survey by the American Academy of Dermatology, 98% of respondents recognized the dysplastic naevus as a distinct entity (2373).

Epidemiology
The estimated total number of individuals affected by the familial form is approximately 32,000 in the United States (1320). Sporadic, histologically dysplastic naevi are seen in up to 50% of White adults, depending on how the lesion is defined (535,571,1828). The estimated prevalences of dysplasia in a population-based series of naevi ranged from 7-32% (1829). The prevalence of clinically defined dysplastic naevi also varies according to the criteria used, ranging from 5–20%.

Etiology
Ultraviolet radiation has been implicated in the genesis of dysplastic naevi and melanoma. Noy et al found higher in vitro sensitivity to DNA damage by ultraviolet B radiation in melanocytic naevus cells compared to foreskin melanocytes (1732). One recent study found an increased relative risk for melanoma in a dysplastic naevus group with poor in vitro DNA repair capacity (1360).

Localization
Dysplastic naevi can occur anywhere on the body but are most commonly found on the trunk (496). In females, there may be a considerable number on the legs (5559). A “quadrant” form of dysplastic naevus distribution has been reported where a 59-year-old man had numerous aggregated pigmented lesions (common acquired naevi and dysplastic naevi) confined to the left upper quadrant of his body. Within this quadrant, two malignant melanomas at different stages of progression developed from dysplastic naevi (2266). Hidden areas such as the scalp and genitalia need thorough evaluation as dysplastic naevi may be seen in these areas (731,2029). In Greene’s original description, it was noted that unlike ordinary moles, dysplastic naevi are often found on the scalp, buttocks and female breast (897). Lesions on the scalp, genitalia and upper back should be considered for excision due to the difficulty with patient self-examination of these locations (749), although careful follow-up is a reasonable alternative.

Clinical features
Patients may have one, several or up to hundreds of lesions. In one study, patients who had DN outside the familial melanoma setting had an average of 10 per person (157). The clinical features originally ascribed to DN included ill-defined or irregular border, irregularly distributed pigmentation, background erythema, and size greater than 5 mm (496,2029). Lesions often differ from one another in the same individual and in addition, they are often different between individuals (778). Some lesions may have a central papular component with a macular flare that blends into surrounding tissue resulting in an ill-defined, fuzzy periphery. The surface texture has been described as “pebbly” (2476). Other lesions are macular or plaque-like without a central papule or nodule. Irregularities in pigment range from tan to dark brown to black. There are often areas of pink and some lesions are amelanotic. Characteristically, lesions first appear around the time of puberty and if they are not apparent by age 20, it is unlikely that an individual has the familial melanoma/dysplastic naevi trait (897).

Diagnostic criteria
The Dutch Working Group produced five
Melanocytic tumours

...ing dysplastic naevi, the vast majority of dysplastic naevi may arise within preexisting naevi on the scalp, 4) one naevus on buttock or > 2 on dorsa of the feet, 5) > one iris naevus. Individuals who have three or more points are considered to have the dysplastic naevus syndrome phenotype (1700).

Dermoscopy and imaging

Dermoscopy can be used to assist in differentiating a DN from other benign or malignant lesions. A lesion that does not demonstrate features of the predominant type of naevus seen in that individual should be considered atypical and receive special attention (1043). This is analogous to the “ugly duckling” lesion that refers to one that is distinct from others in a given patient. It has been recommended that such lesions be biopsied as they are more likely to be the ones that demonstrate features suggestive of melanoma (900).

Several studies have demonstrated the usefulness of regular whole body photographs (1474) and computerized imaging for melanoma surveillance (387, 1286,2440).

Progression to malignant melanoma

Although melanomas in patients with dysplastic naevi may arise within preexisting dysplastic naevi, the vast majority arise de novo. Histologic changes indistinguishable from those of dysplastic naevi are often observed at the periphery of primary melanomas not associated with naevi and such findings have been interpreted as representing “precursor” dysplastic naevi (672).

Dysplastic naevi may have chromosomal instability and poor repair mechanisms after sunlight induced injury (1067,2128). Landi et al demonstrated an increased relative risk for melanoma in a dysplastic naevus group with poor in vitro DNA repair capacity (1360). Elder classified 6 stages of tumour progression via monoclonal antibodies to melanoma cells or their extracts on frozen tissue sections (675A).

Histopathology

Definition and description

The major histopathologic criteria include architectural and cytologic features: size ≥4 mm, junctional component often adjacent to a compound naevic component, nested and single melanocytes mainly near the tips and sides of elongated rete ridges, stromal reactions and mild to moderate cytologic atypia.

There is lack of consensus regarding the histologic classification of dysplastic naevi. Historically, some groups advocate that atypical architecture is all that is required to establish the diagnosis (1943,1980), while others require cytological abnormalities (1925). Shea et al recommend evaluating both cytology and architecture in the diagnosis of DN (2158). More recent descriptions of features common in DN histology included a central dermal naevocytic component with a peripheral extension of a junctional component, elongated epidermal rete ridges, bridging of nests of melanocytes at the dermo-epidermal junction, nests of melanocytes at the sides of rete ridges as well as at their bases, and concentric eosinophilic papillary dermal lamellar fibrosis (1943). Ackerman and others have placed emphasis on the “shoulder phenomenon” which describes peripheral extension of the junctional component beyond the dermal component in dysplastic naevi (18,1828).

In general, histologic criteria involving architecture used to describe dysplastic naevi include: circumscription, symmetry, cohesion, suprabasalar melanocytes, confluence and single cell proliferation. Cytologic features include: nuclear shape and staining, nuclear size, nucleolar prominence, and cell size (2158).

One of the problems in the definition of these lesions is that the histologic changes are non-specific and may be seen in a number of other naevi without clinical features of “dysplastic” naevi such as growing naevi in children and naevi located on certain anatomic sites such as the scalp and flexural areas. Furthermore, the definitions used to describe cytologic atypia are subjective.

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<tr>
<td>Dermoscopy finding</td>
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<tr>
<td>Pigment network</td>
</tr>
<tr>
<td>Overall pigment</td>
</tr>
<tr>
<td>Brown globules</td>
</tr>
<tr>
<td>Margin of pigment network</td>
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<tr>
<td>Black dots</td>
</tr>
<tr>
<td>Radial streaming</td>
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<td>Pseudopods</td>
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<td>Depigmentation</td>
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<th>Table 2.11</th>
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<tr>
<td>Clinical characteristics of dysplastic naevi</td>
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<tr>
<td>&gt;Variable size (&lt;5mm-over 1 cm): great intralesional variation with respect to size</td>
</tr>
<tr>
<td>&gt;Irregular colour: irregular browns, red papule with brown halos, speckled</td>
</tr>
<tr>
<td>&gt;Irregular contour: macular or macular with central papular component</td>
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<tr>
<td>&gt;Ill-defined border, often “fuzzy”</td>
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<td>&gt;Preferential location on the trunk</td>
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as in no case are the atypical cytologic features as frankly atypical as seen in fully developed melanoma.

**Immunoprofile**

Mild to moderate staining of dysplastic naevi is observed using antibody to HMB45 antigen. This antibody also often stains intradermal melanocytes within melanomas but not as strongly in common melanocytic naevi (2214). S-100 is a protein found in the central nervous system that is also present in melanocytes, including melanoma. S-100 protein is found at the dermo-epidermal junction and at all levels of the dermis in dysplastic naevi (1792). However, S-100 staining is non-specific as it is seen in common naevi, dysplastic naevi as well as malignant melanoma.

**Growth fraction / MIB-1 index**

Some authors assert that the presence of the proliferation marker Ki-67 in dysplastic naevi indicates that these lesions are precursors to melanoma (760). The percentage of cells that expressed Ki-67 was an independent prognostic factor (1308). Kanter et al found that percentages of MIB-1 immunoreactivity in the intradermal portion of the lesions was negligible for benign congenital and acquired naevi, as well as in dysplastic naevi compared to melanomas which exhibited a markedly increased proliferative activity, especially vertical phase melanomas (1201). At the current time, it is not recommended that proliferation markers be used as a reliable method for distinguishing between naevi and melanoma.

**Electron microscopy**

The melanosomes in epidermal melanocytes in dysplastic naevi are abnormal, with incompletely developed lamellae and uneven melanization (2476). Abnormal spherical and partially melanized melanosomes similar to those observed in superficial spreading melanoma have been observed by electron microscopy (672,1363). Based on these transmission electron microscopy findings, one group suggested that dysplastic naevi lie on a continuum between naevi and superficial spreading melanoma. No correlation has been shown prospectively between ultrastructural findings and progression or predilection to the development of MM.

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**Fig. 2.57** Dysplastic naevus. A The naevus cell nests are confined predominantly to the tips of the rete pegs. B Note the cytological atypia with nuclear hyperchromasia.

**Fig. 2.58** Dysplastic naevus. A The junctional component shows both architectural and cytological atypia. There is a mild, superficial perivascular lymphocytic infiltrate. B Mild atypia of the junctional nests and dermal papillary fibroplasia. These is some melanin incontinence.
Variants
Toussaint and Kamino observed histopathologic changes of "dysplastic" naevi in other types of naevi. They also noted that some dysplastic naevi demonstrated features of other varieties of naevi. 2,164 cases of compound melanocytic naevi that fulfilled the histopathologic criteria for the diagnosis of compound dysplastic naevus were reviewed. 87.6% had the histopathologic characteristics of dysplastic naevus, 8.3% showed a dermal component with a congenital pattern, 3.1% demonstrated epidermal and dermal characteristics of Spitz naevus, 0.3% had features of a combined blue naevus, 0.6% had a halo phenomenon and 0.1% showed intradermal naevus. The authors advocate describing dysplastic melanocytic naevi by categorizing them into six groups: 1) dysplastic naevus; 2) dysplastic naevus with a congenital pattern; 3) dysplastic Spitz naevus; 4) dysplastic combined blue naevus; 5) dysplastic halo naevus; and 6) dysplastic neuronaevus.

Differential diagnosis
The clinical differential diagnosis of dysplastic naevi includes congenital melanocytic naevi, pigmented basal cell carcinoma, Spitz naevus, common acquired melanocytic naevi, melanoma in situ, and superficial spreading malignant melanoma. The histologic differential diagnosis includes melanoma, recurrent naevus, halo naevus, congenital naevus, a growing naevus in a child and Spitz naevus.

Grading
Some authors emphasize cytologic criteria for grading dysplastic naevi (1925). In 1993, Duncan et al advocated grading dysplastic naevi into groups based on cytology. Dysplastic naevi with slight, moderate and severe cytologic atypia were differentiated. However, concordance between experienced dermatopathologists ranged from 35% to 58%. Because of lack of reproducibility, DeWit et al. did not recommend grading atypia in dysplastic naevi (612). An analysis of 12 histologic parameters in 123 dysplastic naevi failed to identify parameters useful in differentiating mild from moderate dysplasia (1854). Despite these considerations, melanoma risk has been associated with the degree of atypia in dysplastic nevi (102).

Somatic genetics
Cytogenetics and CGH
Jaspers et al performed cytogenetic investigations on lymphocytes and fibroblasts from 25 individuals with dysplastic naevus syndrome and compared the results with a a control population of clinically normal relatives and unrelated individuals. In five DNS patients, increased frequencies of cells with random chromosomal rearrangements including translocations and inversions were observed. These abnormalities were absent in the control population (1134).
Caporaso analyzed the karyotypes of 163 family members from 13 melanoma-prone families to investigate whether chromosomal instability contributes to familial melanoma. Cutaneous malignant melanoma and dysplastic naevi syndrome patients each had increased structural and numerical abnormalities compared with pooled controls (377). However, the criteria used to define lesions as "dysplastic" naevi were subjective from the outset so the validity of such studies remains in question.
Park and Vortmeyer examined the frequency of p16 and p53 deletion in nine dysplastic naevi and 13 benign intradermal naevi with five microsatellite markers. Hemizygous deletion was detected in seven of nine dysplastic naevi at one or more loci for p16. No loss of heterozygosity was detected in any of the benign intradermal naevi (1775).

Molecular genetic alterations
Greene performed an extensive review of the genetics of malignant melanoma and dysplastic naevi in 1998. Many studies demonstrate an autosomal dominant mode of inheritance and speculate pleiotropic manifestations of a proposed melanoma gene on chromosome 1 (1p36). CDKN2A, a tumour suppressor gene localized on chromosome 9, is also reported to be a melanoma gene. The relationship of melanoma to mutation of CDKN2A has been confirmed (895). Hussein evaluated skin tissue samples of melanoma, dysplastic naevi and benign melanocytic naevi for microsatellite instability. Microsatellites are short single sequence motifs repetitively scattered throughout the human genome. The variation in microsatellite pattern length between tumourous and matching non-tumourous tissues is referred to as microsatellite instability. Microsatellite instability has been associated with other familial and sporadic tumours. Hussein's results demonstrated MSI at 1p and 9p chromosomal regions in dysplastic naevi.
and malignant melanoma but not in benign naevi lending further support to others that have speculated on the presence of “melanoma genes” involving the short arm of chromosomes 1 (1p36) and 9 (9p21) (1087). In 2002, Tucker provided 25-year prospective data regarding 33 families with familial melanoma and dysplastic naevi. Seventeen members were found to have mutations in CDKN2A. Tucker found that the majority of clinically diagnosed dysplastic naevi remained stable or regressed over time. The majority of melanomas detected over the course of the study arose from naevi although some arose de novo (2384).

**Genetic susceptibility**

As discussed above, Clark originally described dysplastic naevi in relation to a familial syndrome called the B-K mole syndrome (496). Most dermatologists agree that family members of patients with dysplastic naevi need evaluation (2373). Familial dysplastic naevi and melanomas have rarely been reported with other systemic malignancies involving the central nervous and digestive system (129,213).

**Prognosis and predictive factors**

The incidence of melanoma developing in a given dysplastic naevus has been estimated at 1:3000 per year. Therefore, dysplastic naevi should not be considered as high risk precursors of melanoma, but rather as markers that allow identification of individuals at increased risk for melanoma.

**Number of dysplastic naevi and family history**

Patients with greater numbers of naevi, dysplastic or otherwise, are at greater risk for melanoma (2386). Dermatologists acknowledge patients with multiple dysplastic naevi, especially if there is a personal or family history, are at greater risk for developing melanoma (2373). If patients are from “melanoma-prone families” and have clinically dysplastic naevi, as defined by criteria that include lesion-al diameter, their individual risk for developing a melanoma is several hundred times that of the general population, with a risk for lifetime incidence of melanoma approaching 100% (744,846). The significance of a single histologically dysplastic naevus in this context has not been determined. One study evaluated patients with an established diagnosis of melanoma (n=716) compared with normal controls (n=1014) and found that one clinically dysplastic naevus was associated with a 2-fold risk, while 10 or more conferred a 12-fold risk of melanoma (2386). In the same study, patients who bore 100 or more clinically non-dysplastic naevi had a relative risk of 3.4. Approximately 50% of dysplastic naevi patients with a family history of MM may have multiple primary melanomas (1320).

**Histopathological criteria**

There is evidence that histological atypia does correlate with melanoma risk. A recent study of more than 20,000 naevi divided them microscopically into mild, moderate, or severe categories of dysplasia. A personal history of melanoma was present in 5.7 of the patients with mild, 8.1 with moderate and 19.7 with severe atypia. It was concluded that the risk of melanoma was greater for persons who tend to make naevi with high-grade histological atypia (102).

**Genetic predictive factors**

Currently, there are no commercially available genetic tests that would be predictive of dysplastic naevi progression to melanoma.
In some anatomic sites, naevi may have atypical histological features. This chapter discusses three clinicopathologic entities: acral, genital and Meyerson naevi, but other site specific features have been described, including naevi occurring in flexures, umbilicus, ear and scalp.

**Acral naevus**

**Definition**
Acral naevi (AN) are benign melanocytic proliferations from the palms and soles.

**Synonyms**
AN or “naevi on volar skin” include histologic subtypes termed “Melanocytic Acral Naevus with Intraepidermal Ascent of Cells (MANIAC)” (1545) and “atypical or acral lentiginous naevus” (501,1511).

**Epidemiology**
Clinical studies which are unable to distinguish lentigines from true naevi, record discrete pigmented volar lesions in less than 1 to 92% (1416) of subjects, with most studies suggesting a range of 3 – 41% of the population (63,519,1338,2223,2418). In a histologically confirmed study, 3.9% of Caucasians had AN (1473). Darker patients tend to have a greater percentage (519,1763) and higher total of naevi on acral surfaces (63,519,1553,2418), though this is not always found (574,1416). Pigmented acral lesions are generally more common in the second and third decades (63,1338,1415,2418).

**Localization**
Plantar naevi are probably more common than palmar naevi (63,574,1473,2418). AN may occur on both pressure-bearing and pressure-spared surfaces (45,63,1415).

**Clinical features**
AN are usually less than 8 mm with a light to dark brown striated macular component. Congenital AN can be particularly difficult to clinically distinguish from melanoma (289,1511,2013,2017,2018). On epiluminescence microscopy (ELM) dermatoscopy, the pigmentation of AN is accentuated in dermal glyphic furrows and occasionally around eccrine ostia, thereby creating reproducible patterns (45,1232,2014,2015). In acral melanomas the pigment is distributed along the dermatoglyphic ridges (45).

**Genital naevus**

**Definition**
Melanocytic naevi on the perineum and genitalia, hereafter “genital naevi (GN)”, include different naevic types distinguished and united by unusual, variably present junctional features.

**Synonyms**
A subgroup of GN with "unusual histologic features" (480,782) or "atypism" (1608) have been dubbed "atypical melanocytic naevus of the genital type (AMNGT)" (495)

**Epidemiology**
About 10% of men and women have pigmented genital lesions (574,784,1955), but many are lentigines (784,1955). Histologically confirmed GN occur in 2% of women (267,480,1955). AMNGT comprise a minority of all GN (267,480,1955). They typically present by the twenties (1608) and, in contrast to vulvar melanoma, are seen exclusively in premenopausal women (1608,2015). Dysplastic naevi may also occur on the genitalia but they are usually observed in people with dysplastic naevi elsewhere on their bodies (267,1608). Vulvar naevi were said to have increased premalignant potential (1763), though recent data...
refutes this (1954). Histological studies suggest that from 1% (391) to 12% (495) of vulvar melanomas are associated with a naevus.

Localization
AMNGT are more commonly seen on the labia minora and clitoris (495). Although infrequent, AMNGT may occur on male genitalia (495). Naevi with histologic features similar to AMNGT may be observed on flexural sites and along the vestigal “milk-line” from the axilla to the upper thighs (1964). Dysplastic naevi more commonly occur on the labia majora and perineum (495).

Clinical features
Common type GN are dome shaped, evenly pigmented, tan to dark brown papules less than 1 cm (1955). Both AMNGT and dysplastic GN can be polypoid or flat (495). They are usually tan-brown, often with some black areas (495). Clark et-al report a size range from 2 to 24 mm (495). Despite a long history of advice to the contrary, prophylactic removal of all genital naevi is not recommended (480,784,1955). AMNGT observed from 1 to 16 years have not recurred or metastasized; yet, their conservative reexcision has been advised (495).

Etiology
The genesis of GN is poorly understood. Possible influences include repeated superficial trauma, sex hormones, genetic determination and stroma type (391, 495,1964).

Histopathology
AMNGT are typically “mushroom shaped” with a base composed of maturing melanocytes similar to a common naevus. Melanocytes at the dermal-epidermal junction are arranged in one of three patterns: nests; dyshesive nests; and crowded, ill-defined nests and single melanocytes. In about half of AMNGT there are “skip areas” at the dermo-epidermal junction which lack melanocytes. Thus, it is the junctional component in AMNGT which is worrisome for melanoma. Unlike dysplastic naevi, AMNGT usually lack a lymphocytic infiltrate. The “ill-defined” stroma of AMNGT is different from that typically seen in melanomas or dysplastic naevi (495). The histopathologic features of dysplastic GN are similar to dysplastic naevi elsewhere (267,495,1955). Rarely, genital naevi may be distorted by coexistent lichen sclerosus et atrophicus, producing histologic changes similar to those seen in recurrent naevi (17,352,390). Unlike melanomas, vulvar naevi are said to lack intraepidermal ascent of melanocytes (17,24,391,782), though this has been disputed (984,1608). Regardless of subtype, GN differ from melanoma by circumscription, matura-
tion, and symmetry (17,24,391,782).

Meyerson naevus

Definition
Meyerson naevus is a benign naevus of junctional, compound or intradermal type surrounded by an eczematous halo (2478).

Synonyms and historical annotation
"Spongiotic change in melanocytic naevi" (2478), halo dermatitis (352,2330), halo eczema (1329) and perinaevic eczema (1816). The eponym "Meyerson naevus" (MN) was suggested (1706) to honour the 1971 description of a spongiotic dermatitis involving melanocytic naevi (1595).

Epidemiology
MN typically occur in young adults (1706) and children (2167). Affected men have been reported about three times more frequently than women (1706).

Localization
Eczema may involve one or several naevi (1329,1706) and may spread beyond naevi to previously normal skin (306, 729). There are no clinical features to suggest which naevi become dermatitic (1329,1706).

Clinical features
The change may involve one or more naevi simultaneously. The naevus does not usually undergo regression as a result of this change although the transformation of a Meyerson naevus into a halo naevus has been recorded once (1884). MN are characterized by a pruritic, raised erythematous, scaling and crusted plaque which extends symmetrically 1–2 cm from the central naevus (306, 1329,1595). Upon resolution the naevus persists unchanged (1595,2330), though post-inflammatory hypopigmentation may occur (1595,2330).

Etiology
The inflammation of MN has been likened to pityriasis rosea (564,1595) and allergic contact dermatitis (2478). One case was triggered by interferon alpha (1328).

Histopathology
MN are characterized by spongiosis,
microvesiculation, irregular acanthosis, parakeratosis, focal crust and a superficial perivascular infiltrate of lymphocytes and eosinophils (306,676,1595,2478). There is no histologic regression nor depigmentation (2478). There is a naevocellular naevus of junctional, compound or intradermal type with an associated subacute spongiotic dermatitis (1706). There is variable epidermal acanthosis and a mild to moderate superficial perivascular and interstitial infiltrate of lymphocytes. Usually there are a few eosinophils. There is often mild exocytosis of lymphocytes into the epidermis. There is no regression, although one exception has been recorded (see above). Rarely, dysplastic naevi have been involved (676,1328).

**Immunoprofile**
Lymphocytes in MN are predominately CD4 positive (729,1816). ICAM-1 has been reported to be increased on keratinocytes and endothelium within MN (717).
Persistent (recurrent) melanocytic naevus

Definition
Persistent melanocytic naevi are benign compound or intradermal melanocytic naevi that persist (recur) after incomplete excision.

Synonym
Pseudomelanoma (1310)

Clinical features
Persistent melanocytic naevi are the result of incomplete removal after superficial shave technics, dermabrasion or laser treatment (271). The lesions ‘recur’ usually after weeks or months after therapy. They are characterized by variably pigmented macules, papules or plaques with irregular borders. A scar from previous surgery can be usually recognized.

Histopathology
Scanning magnification shows commonly above a dermal melanocytic naevus a scar with fibrosis. The intraepidermal changes are characterized by sharp circumscription and confluent nests of melanocytes, that are not equidistant and vary in sizes and shapes. The nests are mostly situated at the dermo-epidermal junction. Melanocytes are also arranged as solitary units at the dermo-epidermal junction and sometimes above it in upper layers of the epidermis (1037).
Assessment of the original specimen is very important for an accurate diagnosis to ensure that the lesion is really a persistent melanocytic naevus and not a persistent melanoma.

Differential diagnosis
The features within the epidermis and in epithelial structures of adnexa may simulate a melanoma in situ. However, the sharp circumscription of the intraepidermal component, the presence of melanocytes in nests and as single units mostly at the junction and the typical naevoid cells of the preexisting dermal melanocytic naevus beneath a scar are helpful clues to the diagnosis of persistence (recurrence). Furthermore in persistent melanocytic naevi the melanocytic proliferation within the epidermis is confined to the area above the scar.
Definition
Spitz naevus is a benign proliferation of large spindled, oval or large round (epithelioid) melanocytes that begins in the epidermis, and evolves into compound or intradermal stages. This distinguishes it from some forms of blue naevus, in which the lesion is wholly intradermal from the outset.

ICD code
8770/0

Synonyms
Spindle and epithelioid cell naevus, naevus of spindled and/or epithelioid cells, benign juvenile melanoma (2239). Pigmented spindle cell naevus (Reed) is probably a distinctive variant of Spitz naevus (158,162,2005).

Epidemiology
Spitz naevus is most common in the first two decades of life (1015,2155). Accurate population based studies on its prevalence are not available, and are coloured by the caution shown by pathologists in making an outright diagnosis of Spitz naevus in middle aged or older adults, and in making a diagnosis of Spitz naevus in young adults if there are any unusual microscopic features. Spitz naevi are mostly recorded in Caucasian patients. However, they occur in all racial groups, and their occurrence in Asians and Africans may be underestimated.

Localization
Spitz naevi can occur on any areas of the body, although the face of children and thighs of young women are stereotypical associations.

Clinical findings
The earliest recognizable Spitz naevi are about a mm. or so in diameter, and the largest recorded are over 2 cm. While the criterion of size has been popularized in the differential diagnosis between Spitz naevus and melanoma, many Spitz naevi are over 1 cm. in diameter. There appears to be an initial period of rapid growth, followed by stabilization. This is in contrast to melanoma, in which the diameter of the lesion is seldom stable. Most Spitz naevi are lightly pigmented. The classic lesion is a pink to red papule, with an even round border and a domed shape. There is slight scale. The degree of erythema is often such that the clinician considers the diagnosis of haemangioma. However, if one looks at the initial description by Spitz, it is clear that there is considerable heterogeneity, with tan and medium or even dark brown lesions, and verrucous ones also possible (2239). In dark skinned people, Spitz naevi are usually darker than their normal skin colour. There is usually a uniformity of pigmentation, with the notable exceptions of combined Spitz naevi and Spitz naevi with a halo reaction. Ulceration is practically never present in Spitz naevi, except in children who traumatize them in play or excoriate them. The presence of an ulcer outside of these settings merits reconsideration as melanoma.

Most Spitz naevi are single lesions. However, groups of Spitz naevi can occur in a single area in agminated Spitz naevus (44,2002). In such cases, the epidermis in between the papules of Spitz naevus can be normal in appearance, or more commonly is lightly pigmented, resembling a café au lait spot (when it occurs in Caucasian patients). In eruptive Spitz naevus, a patient may have many papules of Spitz naevus appear on a limb or even over the entire integument within a few weeks or months. This obviously distressing situation can be confused with metastasis of melanoma.

Etiology
The cause of Spitz naevus is unknown. Sunburn and biopsy of a single Spitz naevus have been linked to eruptive lesions (597).

Histopathology
Because the findings of Spitz naevus differ significantly at various stages, we will describe those in detail. Spitz naevus begins as a proliferation of large oval melanocytes at the dermal-epidermal junction. This can occur along a front of only a few mm., and is first recognizable by single, large melanocytes with abundant eosinophilic cytoplasm and large vesicular nuclei. There are often a large number of cells with several nuclei, even in small lesions. Cytoplasm is abundant, and even though the nuclei may be large, they are usually monomorphous. Clefts demarcate the melanocytes from adjacent keratinocytes. Even if single cells are present in number above the junction, they are evenly distributed (355). As these lesions enlarge, the epidermis above the proliferation thickens, and nests begin to form. The epidermal thickening is largely via hyperplasia of the spinous layer, with squamatization of the basal layer and pointed rete ridges.
There is corresponding hypergranulosis and compact hyperkeratosis.

Within the junctional nests of a Spitz naevus are clefts, separating the melanocytes from one another, and from the epidermis. The clefts tend to be prominent over the apices of junctional nests. The nests may appear to be embedded in the epidermis, rather than lying at the bases of rete ridges. The epidermal hyperplasia of a well developed junctional Spitz naevus, and the nests of the naevus itself are both well circumscribed (19, 1636, 1638, 1769, 2479). By the time that nests are of substantial size, one may encounter Kamino bodies in the epidermis. Kamino bodies are dull pink staining globules, up to the size of several keratinocytes, often with a scalloped border and a periphery in which there are crescent shaped, compressed appearing keratinocytes (1186). Unlike dyskeratotic cells, which are more brightly eosinophilic, their major ingredient is basement membrane material. They stain with PAS-D and with immunoperoxidase stains for basement membrane components, such as laminin and type IV collagen (2499).

Compound Spitz naevus forms when junctional nests become incorporated into the dermis. In early compound lesions, one may see a dense lymphocytic infiltrate, rather than the sparse perivascular one that most authors describe. The dermal nests tend to be smaller than the junctional ones, and as melanocytes descend into the reticular dermis, one can discern a gradient from large nests to smaller ones, and single cells may predominate at the base. Mitotic figures can be present in the upper part of a compound Spitz naevus, but tend to decrease in number toward the base of the lesion. Maturation of melanocytes is also a correlate, with smaller cells that have less cytoplasm, smaller nuclei, and smaller and less eosinophilic nucleoli all findings that reassure the pathologist. If a Spitz naevus is pigmented, the pigmentation lessens in the lower half of the lesion. Fully formed compound lesions often have a domed surface and a wedge shape. Unlike the case in early compound, or even junctional lesions, lymphocytic infiltrates are usually sparse and perivascular.

Intradermal Spitz naevi preserve the domed/wedge shape noted above. The epidermis is often slightly hyperplastic.

The nests of melanocytes are often present between thickened collagen bundles in the lower part of the lesion. When this is prominent, some apply the term desmoplastic Spitz naevus. Unlike the case in desmoplastic melanoma, there are no markedly elongated fascicles of cells. If the proliferation abuts the subcutis, one may see lymphoid nodules. For both compound and intradermal lesions, an important finding is that the nests at each level of the lesion should be similar in size, with the cells similar in overall and nuclear size and in pigmentation.

There are many important variants of Spitz naevus. On acral skin, one may see many single melanocytes scattered above the junction. A halo reaction may be present, sometimes accompanied by a clinical halo. The lymphocytes are evenly dispersed throughout the lesion, and some may be apposed to pyknotic melanocytes. The stroma may be sclerotic (hyalinizing Spitz naevus) or highly vascular (2293). Some nests may have an empty appearing centre (tubular Spitz naevus) (2228). In combined Spitz naevus, other populations of melanocytes (e.g. small round, bipolar-dendritic, balloon, etc.) may be present (1961). This is one of the most difficult variants to deal with, as the large cells may not mature and dense lymphocytic infiltrates (up to a halo reaction) may be present (972).

Another difficult variant is persistent Spitz naevus. The great majority of Spitz naevi do not recur at the biopsy site if the lesion seems to be removed clinically, but goes to a margin. Those that do can show suprabasal scatter of melanocytes (as in other recurrent naevi), a compound Spitz naevus over a scar, a nodule next to a scar, or a picture resembling desmoplastic Spitz naevus (969).

Lastly, there is a “grey zone” of lesions in which there are many findings of Spitz naevus, but the diagnosis is less certain. For lesions in which the diagnosis is Spitz naevus, but there are a few findings that are unusual, many use the term “atypical Spitz naevus”, although this may be attacked on semantic and functional grounds. If one is not sure of the diagnosis, a descriptive term, such as “proliferation of large melanocytes involving the epidermis and dermis” is preferable. This should be accompanied by a note or comment explaining the difficulties, differential diagnosis, including if appropriate, microstaging parameters that would be appropriate if the lesion were regarded as melanoma, and advising reasonable management. The role, if any for sentinel lymph node biopsy in difficult cases is currently considered controversial (1444, 2286).

Among these “grey-zone” lesions is an emerging, relatively homogeneous group of lesions with a distinctive pattern, often...
found from early childhood to young adulthood in which there are some features of Spitz naevus and others of melanoma. Common denominators include a vertical orientation, extension into the subcutis with no diminution in cellularity and a blunt, multinodular interface, ulceration, a plasmacytic infiltrate and deep mitotic figures. Such cases have been described as “malignant Spitz naevus” and also simply regarded as melanomas (2205). In the initial study of “malignant Spitz naevus” there were 3/32 lesions in which palpable lymph node enlargement had occurred, and another 3 in which lymph node involvement was detected on elective dissection. Very similar lesions have been described as melanomas in children (1632). Follow up data has been presented to the effect that systemic metastasis may not occur, or may be much less frequent than in adults with conventional melanomas matched for thickness. Clearly, further studies are needed to determine if these lesions are fundamentally Spitz naevus, melanoma, or neither.

**Somatic genetics**

While most cells in most Spitz naevi seem to be diploid, there are a proportion of polyploid cells, at least in the upper part of lesions as judged by image analysis cytometry (1386). True aneuploidy may be uncommon, as evaluated by flow cytometry (2439). In an analysis using comparative genomic hybridization the majority of Spitz naevi did not show chromosomal aberrations, whereas 25% showed an isolated gain of chromosome 11p (174). Preliminary studies indicate that the increased copy number of chromosome 11p is due to the formation of an isochromosome 11p (1494). About 70% of the Spitz naevi with increased copies of chromosome 11p have mutations in the HRAS gene which maps to this location (172). HRAS mutations have been found only in a minority of cases (<10%) with normal copy number of chromosome 11p. Preliminary studies indicate that mutations in BRAF occur infrequently in Spitz naevi.
Pigmented spindle cell naevus (Reed)

Definition
Pigmented spindle cell naevus (Reed) is a benign melanocytic naevus showing dark pigmentation clinically, and a proliferation of spindled melanocytes histopathologically.

ICD-O code 8770/0

Synonyms and annotation
This melanocytic naevus has been named eponymously after Richard Reed, who described it in 1975 (1909). It has also been referred to as Reed naevus or Reed tumour. While some authors regard it as a subtype of the Spitz naevus, pigmented spindle cell naevus (Reed) presents with peculiar clinical and histopathologic features, allowing a reproducible diagnosis and classification to be made.

Epidemiology
Pigmented spindle cell naevus (Reed) is a melanocytic tumour found in children, adults, and, rarely, older patients, with a peak in the third decade. There is a predominance for females.

Clinical features
The patients present with a darkly, homogenously pigmented, flat or slightly dome-shaped, sharply circumscribed papule or plaque located usually on the limbs, especially the thigh (158,2005,2068). Less common locations are the trunk and the head and neck region. The lesions are usually of recent onset and smaller than 1 cm. Surface skin microscopy (dermatoscopy, dermoscopy) reveals typically a "starburst" pattern (characterized by the presence of pigmented streaks disposed in a radial arrangement at the edge of the lesion). A clinical misdiagnosis of malignant melanoma is not infrequent, due to the dark pigmentation and recent onset of the lesions.

Histopathology
Histologically, the tumours are symmetrical and show a sharp lateral circumscription. Spindled, pigmented melanocytes arranged in vertical nests at the dermo-epidermal junction predominate (158,2005,2068). A few, and in some instances many, melanocytes may be seen above the dermal/epidermal junction, as well as confluence of the nests. The proliferation of melanocytes may be confined to the epidermis, or may extend into the papillary dermis. Occasional mitoses may be found. Cytomorphologically there is a uniform proliferation of elongated, fusiform melanocytes, usually without atypical features. The nuclei are relatively small, with uniform, delicate chromatin. Epithelioid melanocytes are admixed in a minority of cases. Commonly, the epidermis is slightly hyperplastic and shows marked hyperpigmentation of the basal keratinocytes. Intraepidermal eosinophilic globules (so-called "Kamino bodies") can be observed in about half of the cases. An inflammatory infiltrate composed of lymphocytes and histiocytes with many melanophages is found within the papillary dermis. A subset of cases shows a considerable overlap with Spitz naevi. Cases with some cytological atypia have been termed "atypical pigmented spindle cell naevus - pigmented spindle cell naevus with architectural and/or cytologic atypia", and may represent a source of problem in differential diagnosis from malignant melanoma (158). A variant described as "plexiform pigmented spindle cell naevus" probably represents a pigmented spindle cells naevus involving the reticular dermis (158).

Prognosis and predictive factors
Pigmented spindle cell naevus (Reed) is a benign melanocytic proliferation with no potential for distant metastases. Local recurrences may be observed in tumours that were incompletely excised.

Fig. 2.70 Pigmented spindle cell naevus (Reed). A Small, flat, dark papule. B Dermoscopy shows the characteristic ‘starburst’ pattern. C Elongated nests at the dermo-epidermal junction and in the papillary dermis; note pigmentation of the basal keratinocytes and melanocytes, and the presence of numerous melanophages in the papillary dermis. D Fusiform melanocytes predominate. Note the mitosis in the upper left corner.
Halo naevus

Definition
A halo naevus presents as a small circumscribed symmetrical, usually papular pigmented lesion with the appearance of a common benign compound naevus, surrounded by a symmetrical area of depigmentation, representing the “halo” (2469). The lesion is defined histologically by the presence of a brisk lymphocytic infiltrate among dermal naevus cells, and by loss of pigment in the epidermis adjacent to the naevus. Some naevi with a lymphocytic response of the type seen in halo naevi do not have an obvious clinical or histologic depigmented halo (948).

ICD-O code 8723/0

Synonyms
Sutton naevus; leukoderma acquisitum centrifugum (2297).

Clinical features
Halo naevi often present during the summer, perhaps because the halo contrasts better with tanned skin. They are most common in teenagers and young adults. In these cases, they are sometimes associated with dysplastic naevi, and are sometimes multiple. Less often, a solitary halo lesion develops in an older adult, and in this circumstance the possibility of melanoma should be ruled out histologically, especially if the central pigmented lesion is clinically atypical or if the halo is eccentric or asymmetrical in contour. Serial follow-up of halo naevi demonstrates a characteristic time sequence, beginning with the appearance of the halo around a compound naevus, followed by fading and disappearance of the naevus. The halo then gradually regains some pigments over a year or two, returning to the appearance of normal skin. During this period, especially in teenagers, other similar lesions may develop.

Studies in patients with halo naevi have demonstrated circulating antibodies that are reactive with neoplastic melanocytes including melanoma cells, and the infiltrating cells have been shown to be mainly T lymphocytes (2090). Antigen-presenting cells and CD8+ T cells have been identified in the inflammatory infiltrates of halo naevi, implicating cytotoxic mechanisms in destruction of naevus cells (2581). Affected individuals also show activated lymphocytes in their peripheral blood (148) as well as T cell clonal expansion (1670) and anti-naevus IgM antibody production (2359). These findings are consistent with the idea that halo naevi represent immunologically mediated rejection of a naevus. The halo develops outside the naevus proper, suggesting that there may be a cross-reaction with a “field” of melanocytes that surrounded the naevus prior to the onset of the intense inflammation in the dermal component.

Histopathology
An early halo naevus presents as a small circumscribed lesion, less then 4 mm in diameter as a rule, composed of naevus cells located in the papillary dermis and usually also in the epidermis. The lesion is symmetrical, and is composed of cells that are uniform from side to side and tend to become smaller (i.e., more “mature”) from the top to the bottom of the lesion. The epidermis may be hyperkeratotic with follicular plugging (2469). The feature that distinguishes a halo naevus from a banal naevus is the presence of a striking dense lymphocytic infiltrate, an appearance that may arouse a suspicion of melanoma in some cases. The lymphocytes extend among the lesional naevus cells, tending to obscure their underlying nested pattern in some cases. Melanin-laden histiocytes and mast cells can be present as well as lymphocytes (2090). Occasional halo naevi contain a few giant cells or there may be a frankly granulomatous response. Over the ensuing weeks or months, the dermal naevus cells disappear and then the histologic differential diagnosis may include lichenoid inflammatory dermatoses. Over a period of a year or two, the inflammatory cells disappear and histologic examination of the site of a completely resolved halo naevus may disclose essentially normal skin, with little or no evidence of scarring or residual pigment (2469). In most halo naevi, there is little or no readily observable melanocytic abnormality in the epidermis at the “shoulder” of the lesion beyond the lateral border of the dermal component, even though it is in this region that the striking clinical halo is located. However, DOPA stains for tyrosinase and immunohistochemical (e.g. Melan-A) or argentaffin stains for melanocytes reveal greatly reduced numbers of them in the area of the halo compared to the surrounding skin (2469).
The lesional cells in most halo naevi are unremarkable dermal naevus cells of the large pigmented (type A) or small non-pigmented (type B) cytology. Pigment is located in naevus cells and in melanophages superficially, and is usually coarse in texture. In some lesions, the dermal cells have nuclei that are larger than is usual in common naevi, and sometimes there is hyperchromatism and a degree of pleomorphism, with or without nucleoli, representing cytologic atypia which is present in about 50% of halo naevi and is usually mild or at worst moderate in degree (1640). This cytologic atypia may represent a form of “inflammatory” or reactive atypia. Mitotic figures are completely absent in most lesions. However, a few lesions judged to be benign halo naevi have shown one or two mitotic figures (1909). Such a finding should provoke careful examination of the lesion to rule out melanoma, with deeper sections and embedding of any residual gross tissue. Findings suggestive of melanoma in a lesion simulating a halo naevus include the presence of a separate population of cells with an expansile pattern of growth, severe uniform cytologic atypia, and/or the presence of frequent mitoses, ulceration or necrosis. The halo phenomenon may occasionally involve other types of naevi, including dysplastic naevi (2370), Spitz naevi (972) and congenital naevi (2359), as well as melanomas (2090), and therefore careful inspection of the underlying lesional architecture and cytology in multiple sections may be required for definitive classification.

The halo region at the periphery of the dermal component of the lesion may contain a few lymphocytes at the dermal-epidermal interface, with a reduction or an absence of identifiable melanocytes. In comparison with adjacent normal epidermis, pigment may be visibly reduced, and this contrast can be enhanced with a melanin stain. In most lesions, there is no intra-epidermal melanocytic proliferation adjacent to the dermal component, but in a few lesions an adjacent component of melanocytic dysplasia may be observed. If an in situ or microinvasive (“radial growth phase”) component diagnostic of melanoma is present adjacent to a dermal lesion simulating halo naevus, the entire lesion is most likely to represent melanoma.

**Differential diagnosis**

The distinction from common acquired or most other types of naevi is usually easy because of the dense lymphocytic infiltrate. The most important differential diagnosis is with melanoma. Compared to nodular melanoma or to the tumourigenic (vertical growth phase) component of superficial spreading melanoma, a halo naevus is usually smaller (the central naevus is usually less than 4 mm in diameter, while most melanomas are larger than 6 mm, though these values are by no means absolute). However, we have rarely observed small melanomas with naevoid characteristics but with diffuse cellular atypia combined with mitotic activity in which diffuse lymphoid infiltration was a prominent pattern. When pigment is present in a halo naevus, it is usually in the form of coarsely divided granules as is the case in most benign naevi, and if there is a junctional component, its character is that of a naevus rather than a melanoma. Thus, there is usually a discontinuous rather than continuous proliferation of predominantly nested rather than predominantly single naevus cells, and there is little or no tendency to single-cell upward (“pagetoid”) intraepidermal spread of the junctional cells.

Some halo naevi may be difficult to distinguish from dysplastic naevi that have an unusually brisk lymphocytic infiltrate. Indeed, not only do halo naevi appear to be common in patients with dysplastic naevi but also a halo response may be seen, clinically and histologically, in dysplastic naevi themselves. If the characteristic patterns of dysplasia are seen at the “shoulder” of the compound portion of a lesion whose other features are consistent with a halo naevus, the diagnosis of dysplastic naevus with halo reaction can be made. Especially if there is a history of other atypical naevi and/or a personal or family history of melanoma, surveillance may be warranted for such individuals.

When naevus cells are inconspicuous among a dense infiltrate of lymphocytes, inflammatory dermatoses such as lichenoid keratoses may be simulated (844). In these circumstances, an S-100, Melan-A or HMB45 stain may reveal the hidden naevus cells. Care must be taken in interpretation, since histiocytes may weakly express S-100, whereas activated melanocytes and melanoma cells may express HMB45. Finally, there are lesions that have an infiltrative lymphocytic response similar to that of a halo naevus but there is no clinical halo. These lesions may be signed out descriptively as “compound (or dermal) naevi with halo reaction” (1909). Conversely, some naevi with a clinical halo may lack a lymphocytic infiltrate of the type seen in halo naevi (812). These may be termed “non-inflammatory halo naevi”.

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**Fig. 2.73** Halo naevus. A Infiltrating lymphocytes are intimately admixed with naevus cells, which will lead to apoptosis and ultimate disappearance of the naevus cells. In later examples, naevus cells are more inconspicuous than they are in this field. B Extending 1 to 2 mm beyond the lateral border of the dermal naevus component, the papillary dermis is widened with slight fibroplasia, there is a patchy lymphocytic infiltrate, and there is absence of pigment and of melanocytes in the overlying epidermis. This region constitutes the clinical halo. C Normal skin adjacent to the halo shows a normal papillary dermis, normal melanin pigment in basal keratinocytes, and the presence of melanocytes, which can be demonstrated if desired with a Melan-A stain.
Appendageal tumours are neoplasms whose differentiation is toward one or more of the adnexal structures of the skin. While mesenchymal tumours of various kinds are technically in this category, conventionally, the term refers to those with origin from, or differentiation toward epithelial adnexal neoplasms. Depending on their presumed origin, adnexal tumours are categorized into those with apocrine and eccrine, follicular and sebaceous differentiation. For most of these tumour types there are benign and malignant counterparts. The histopathological-criteria for prognosis of biological behaviour are well established. The WHO Working Group was aware of recent evidence indicating that basal cell carcinoma (BCC) should be included under the adnexal neoplasms under the term trichoblastic carcinoma. The inclusion of BCC in the chapter on keratinocytic tumours reflects the traditional categorization but does not indicate that the Working Group denies their adnexal origin.
WHO histological classification of appendageal tumours

<table>
<thead>
<tr>
<th>Tumours with apocrine and eccrine differentiation</th>
<th>Malignant tumours</th>
<th>Benign tumours</th>
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1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) [1786] and the Systematized Nomenclature of Medicine (http://snomed.org).

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

TNM classification of skin appendageal carcinomas

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Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

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<td>M 0</td>
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<td>N1</td>
<td>M 1</td>
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Notes:

1 [894,2219].
2 A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.
Appendageal skin tumours: Introduction

Epidemiology
Most studies on adnexal neoplasms have taken place in western countries with Caucasian populations. Benign adnexal neoplasms tend to occur in younger patients than carcinomas do. Adnexal carcinomas vary from those in which actinic damage is the norm, such as the common basal cell carcinoma (which differentiates toward follicular germ) to those that seem to have little relationship to sun exposure (such as spiradenocarcinoma).

Etiology
No known triggering event is evident in the vast majority of adnexal neoplasms. There are some cases in which the cause is an autosomal dominant mutation in a tumour suppressor gene.

Clinical signs and symptoms
Most benign adnexal neoplasms are smooth surfaced, symmetrical papules or nodules the same colour as the patient’s skin or darker. Some, such as sebaceous adenoma and syringocystadenoma papilliferum, have eroded surfaces, but in general, ulceration is a sign of malignancy. Most adnexal carcinomas are irregularly shaped plaques, sometimes ulcerated.

Tumour spread and staging
In general, low-grade carcinomas seldom metastasise; for some, e.g. microcystic adnexal carcinoma, metastasis has not yet been recorded. A haematogenous pattern seems the rule for a few carcinomas, such as adenoid cystic adnexal carcinoma, but most can spread via either lymphatic or haematogenous dissemination. Carcino-mas with eccrine differentiation have a propensity to metastasise to the skin.

Sentinel node biopsy
While a few sentinel node biopsies have been performed for adnexal carcinomas, not enough data have been collected to validate this procedure (274).

Pathology
Diagnostic criteria of adnexal carcinomas
> Irregular borders, asymmetry at scanning magnification
> Horizontal orientation
> Markedly irregular aggregates of epithelial cells
> Necrosis en masse
> Infiltration of the dermis or subcutis without the interposition of densely fibrotic stroma
> Mitoses frequent, can be atypical
> Stroma irregular, often scant, sometimes myxoid
> Nuclei pleomorphic. Some neoplasms with monomorphous nuclei, e.g. microcystic adnexal carcinoma, are exceptions.

Diagnostic criteria of benign epithelial adnexal neoplasms (28):
> Symmetric and smooth bordered at scanning magnification
> Vertically oriented with respect to the surface of the skin
> Aggregates of epithelial cells uniform
> No necrosis en masse (with the exception of poroma)
> Mitoses variable, but typical
> Densely fibrotic stroma, rich in fibrocytes in the case of trichogenic
> Neoplasms forming a blunt, rounded interface with the native dermis. An exception is poroma, which has vascular, myxoid stroma.
> Nuclei monomorphous; rare exceptions include atypical squamous nuclei in poromas.

Immunoprofile
Most adnexal neoplasms are accompanied by variable dense infiltrates of T-cells. These are intimately admixed with the neoplasm (spiradenoma, cutaneous lymphadenoma, adamantinoid trichoblastoma) and lymphoepithelioma-like carcinoma among malignancies are examples. Syringocystadenoma papilliferum has a complement of plasma cells, many of which secrete IgA. A complex array of keratins are expressed in adnexal neoplasms. Those with follicular germinative differentiation express cytokeratins seen in follicular germs in embryonic and neonatal life. Those with ductular differentiation have lumens that stain for carcinoembryonic antigen (CEA), and express simple epithelial keratins. Sebaceous differentiation is characterized by expression of epithelial membrane antigen in a microvacuolar pattern.

Precursor lesions
Benign adnexal neoplasms of various sorts can arise in naevus sebaceous, a malformation involving the epidermis, dermis and adnexae. Otherwise, most benign adnexal neoplasms arise de novo. This is also the case for malignant adnexal neoplasms. Rare apocrine carcinomas arise in naevus sebaceous. Rarely, porocarcinoma, spiradenocarcinoma or hidradenocarcinoma may arise in a pre-existent poroma, spiradenoma, or hidradenoma, respectively. The vast majority of basal cell carcinomas arises de novo. Rarely, basal cell carcinomas occur in pre-existent trichoblastomas.

Histogenesis
The origin of most adnexal neoplasms is unknown. It is better to speak of their differentiation. The most clear-cut evidence of differentiation is in follicular neoplasms, where such signs as follicular papillae and germs (as in the trichoblastomas) or trichohyaline granules (as are focally found in pilomatrixoma and in matrical carcinomas) can occur. Clear-cut apocrine differentiation, in which decapitation secretion of columnar cells that have brightly eosinophilic cytoplasmic granules is also specific. However, there is a marked similarity between eccrine and apocrine ducts. Also, the columnar cells of eccrine secretory coils can resemble poorly differentiated apocrine secretory cells. Hence, neoplasms with ductular differentiation often have debatable histogenesis (1543). To some
extent, the differentiation of neoplasms probably reflects their distribution (1544).

**Genetics**
Approximately one third of sweat gland carcinomas contain TP53 mutations (239A). Otherwise, little is known about the genetics of most epithelial neoplasms, with the exception of those that occur in multiplicity as part of autosomal dominant syndromes (see Chapter 7). The mutations found in the germlines of patients with syndromes and multiple tumour suppressor genes tend to be the same as occur as somatic mutations in sporadic adnexal neoplasms. Some trichoblastomas have mutations in the PTCH gene, as found in naevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Trichilemmomas have mutations in PTEN, the same gene as involved in Cowden syndrome. Mutations in DNA repair genes occur in the sebaceous neoplasms of the Muir-Torre syndrome and, to a lesser degree, in sporadic sebaceous neoplasms.

**Prognosis and predictive factors**
In general, adnexal carcinomas of low cytologic grade have a good prognosis, especially if the lesion is relatively small and completely excised. Those of high cytologic grade may metastasize widely. For many adnexal carcinomas, there are simply insufficient numbers of reported cases to develop much of an idea regarding their prognosis.
Malignant tumours with apocrine and eccrine differentiation

**Tubular carcinoma**

**Definition**
Tubular carcinoma is the malignant counterpart of tubular adenoma, featuring apocrine differentiation with prominent tubular structures.

**ICD-O code**
8211/3

**Historical annotation**
Probably the first reported examples of tubular carcinoma were included in the series of carcinomas of sweat glands published by Stout and Cooley in 1951 (2274).

**Epidemiology**
Tubular carcinoma seems to be slightly more frequent in women. Most patients are middle-aged adults.

**Localization**
The axilla is the most common location, with rare bilateral involvement. Other sites rich in apocrine glands may also be involved (114,127,1705,1785,2274,2397,2460,2569).

**Clinical features**
Tubular carcinoma usually presents as a firm erythematous nodule, which may be ulcerated or adherent to deeper tissues. Tubular carcinomas may arise in naevus sebaceous (644).

**Histopathology**
At scanning magnification, the neoplasm is asymmetric, poorly circumscribed, and infiltrative with prominent and crowded tubular and ductal structures. The lesion often involves the full-thickness of the dermis and it may extend to the subcutaneous tissue. Neoplastic structures show marked variation in size and shape, but, in general, the size of the tubules tends to decrease from superficial to deeper areas. The more superficial larger tubules may show luminal papillations. At higher magnification, epithelial cells lining the tubules show abundant eosinophilic or granular cytoplasm and pleomorphic nuclei, some of them in mitosis. Often the cytoplasm of these cells exhibits signs of decapitation secretion. Lumina are often filled with homogenous eosinophilic material, foamy histiocytes and necrotic debris. Examples of tubular carcinoma may also exhibit focally solid areas with a combination of cribriform or adenoid cystic patterns as additional morphologic expressions. Areas of necrosis en masse are also frequent, but in contrast with adenoid cystic carcinoma, tubular carcinoma shows no deposits of basement membrane material within the aggregations of neoplastic cells and perineural involvement is usually absent. The stroma is sparse. Before a diagnosis of primary tubular carcinoma of the skin is established, the possibility of cutaneous metastasis from a visceral tubular carcinoma should be ruled out.

**Immunoprofile**
Tubular carcinoma shows immunoreactivity with low molecular weight cytokeratins and the luminal cells express EMA and GCDFP-15. Expression of CEA is variable (1785,2569).

**Histogenesis**
The presence of decapitation secretion and continuity between neoplastic tubules and follicular infundibula are signs of apocrine differentiation. This is further supported by enzyme histochemistry.

**Prognosis and predictive factors**
Tubular carcinoma of the skin behaves in a highly malignant fashion. Of the 44 examples reported in the literature, neoplasms from 21 patients metastasized and at least 9 patients died as a result of widespread metastatic disease (1705, 1785,2397,2569).

**Microcystic adnexal carcinoma**

**Definition**
Microcystic adnexal carcinoma (861) is a locally infiltrative and destructive low-
grade adenocarcinoma differentiated toward ducts. It has little capacity to metastasize.

**ICD-O code**

8407/3

**Synonyms**

Sclerosing sweat duct carcinoma (541), eccrine epithelioma, syringomatous carcinoma.

**Clinical features**

The carcinoma occurs on the face of adults, more commonly in women. It affects commonly the face (469) and lip, uncommonly other locations, and grows slowly over a period of months to years. It is similar usually to a depressed scar and rarely causes ulceration.

**Histopathology**

The classical pattern is that of small, superficial, solid to cystic structures that are similar to small infundibular cysts and ducts. In the middle depth, the lesion is composed completely of small ducts, often in very subtle patterns, frequently with involvement of nerves and perineural spaces. In the deepest areas, “Indian” filing and sclerosis are common findings. Thus, there is a sense that the lesion is stratified from superficial (tubules and cysts) to deep (epithelial cords and sclerosis).

Unusual examples contain sebocytic zones (1862), and others contain areas similar to follicular sheath, thus suggesting differentiation toward the folliculosebaceous-apocrine unit. In other cases, the lesions are exclusively ductal, causing some authors to designate them as “syringomatous carcinoma” or “sclerosing sweat duct carcinoma” and suggesting that these examples could be derived from eccrine ducts. Some MACs have solid poromatous or clear cell cytology. Cytologically, the lesions are well differentiated, lacking nuclear pleomorphism or mitotic figures. In fact, the finding of nuclear pleomorphism should cause one to reconsider whether the diagnosis of microcystic adnexal carcinoma is correct.

**Immunoprofile**

There is cytoplasmic staining with AE1/AE3, CK7, and bcl-2. EMA and Ber-EP4 stain in a membranous pattern around ductal cells near the lumen. Alpha SMA and S100 protein stain the

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**Fig. 3.03** Microcystic adnexal carcinoma. Scanning magnification of microcystic adnexal carcinoma illustrates the zonal effect with solid nests and cysts superficially with complex glands deep.

**Fig. 3.04** Microcystic adnexal carcinoma. **A** There are a few cysts and solid nests, but no nuclear pleomorphism. The pattern of the lesion helps to recognize it as carcinoma. **B** Not only are there ducts; there are also strands and small nests of neoplastic cells. **C** This example of microcystic adnexal carcinoma again illustrates the zonation pattern, in this case with a few cysts superficially. Note the deep nests that are present in and around the subcutis; not every case will contain compressed ducts exclusively in the deep zones. **D** This example is similar to some poromas. There are solid nests of monomorphic cells as wells as nests of cells with clear cytoplasm. Some authors have designated these lesions “syringomatous” carcinoma. **E** Despite the striking structural patterns of these lesions, most do not contain nuclear pleomorphism. **F** Peripheral nerve, completely encircled by the neoplasm. Note the ductal space.
tubules peripherally. P53 is positive in less than 25% of the neoplastic cells. There is a low proliferative index, as Ki-67 is positive in less than 5% of the neoplastic cells. CK20, c-erb-2, and CD34 are negative.

**Differential diagnosis**
The principal differential diagnoses are with superficial biopsies of columnar trichoblastoma (desmoplastic trichoepithelioma) or morpheiform basal cell carcinoma (trichoblastic carcinoma), all of which are CK7 negative. Syringoma is a possible consideration in some cases. Rare examples of metastatic carcinoma to the skin can also mimic it.

**Genetics**
There is a single report of a 6q deletion. There is also a report of 2 microcystic adnexal carcinomas, one of which was diploid, and the other, aneuploid, when examined with DNA image cytometry.

**Prognosis**
Treatment is surgical, with microscopic control of margins if possible. Radiotherapy has proven successful rarely, but some reported cases have taken on an even more virulent biology after such treatment.

**Malignant mixed tumour**

**Definition**
Malignant mixed tumour (MMT) is an exceedingly rare cutaneous adnexal carcinoma with a significant risk for aggressive behaviour and a propensity for metastasis. MMT is regarded as the malignant counterpart of benign mixed tumour albeit histological diagnosis is foremost based on the biphasic nature of the neoplasm rather than an admixture of benign mixed tumour remnants with carcinomatous tissue.

**ICD-O code** 8940/3

**Synonyms**
Malignant apocrine mixed tumour. Malignant chondroid syringoma.

**Epidemiology**
MMT represents an exceedingly rare cutaneous adnexal neoplasm which occurs in a wide age range (15 months)
Appendageal tumours

Tubular structures may be either of the elongated apocrine type lined by at least two layers of epithelial cells, with luminal cells exhibiting signs of apocrine secretion and abluminal cells showing plasmacytoid / myoepithelial differentiation, or — more rarely — of the eccrine type showing small round structures lined by a single layer of atypical epithelial cells (961, 1919). Often, however, MMT consists only of solid aggregations devoid of tubules {928, 1919, 2471}. Epithelial tumour cells may either have a deceptively bland appearance (1112,2100) or show distinctive atypia and pleomorphism of nuclei with a high nuclear-cytoplasmic ratio and numerous mitotic figures (1919). Zones of necrosis are common. Characteristic epithelial tumour cells are cuboidal with distinctive polygonal or plasmacytoid features (961, 1919). The latter is considered an indicator of the myoepithelial/apocrine origin of the neoplasm and may be seen as a clue to the diagnosis of MMT (1919).

Electron microscopy

Tumour cells exhibit ultrastructural features of myoepithelia with desmosomes and abundant intracytoplasmic filaments (177,1839,2471). However, ultrastructural studies so far have not presented convincing evidence of either apocrine or eccrine differentiation of MMT (1919).

Variants

MMT may exhibit deceptively bland cytological features (1112,2100) albeit associated with distinctive architectural criteria of malignancy, e.g. asymmetry, poor circumscription, infiltrative tumour margins, and satellite nodules. The recently described malignant mixed tumour related to the sweat gland duct, showing both intraepidermal and dermal components.
by Pinkus and Mehregan in 1963 as epi-
dermotropic eccrine carcinoma (1837).

Epidemiology
Eccrine porocarcinoma is a rare tumour, predominantly observed in elderly patients with an average age of 67 years (1072). Women and men are equally affected. The incidence in one large series was 18 per 450,000 cases (0.004%) (1571).

Etiology
Eccrine porocarcinomas may arise de novo or as a malignant transformation in a pre-existing poroma, hidroacanthoma simplex, or in association with naevus sebaceous (1571,2216,2604). 18 to 50% of eccrine porocarcinomas are associated with pre-existing eccrine poromas.

Localization
Forty-four to 50% of eccrine porocarcinomas arise on the legs, buttocks, or feet (2216). The trunk accounts for 24% of the lesions and the head 18% of the lesions with less frequent lesions located on the upper extremities (1072).

Clinical features
Eccrine porocarcinoma presents as a verrucous nodulo-ulcerative plaque. Clinically the lesions may resemble an eccrine poroma, verruca vulgaris, seborrheic keratosis, melanocytic naevus, fibroma, basal cell carcinoma, squamous cell carcinoma, or pyogenic granuloma. Diagnosis is made by skin biopsy.

Histopathology
Eccrine porocarcinoma forms intraepidermal and dermal nests and cords of epithelial cells with pale cytoplasm. The tumour masses form clearly demarcated and frequently rounded nests of polygonal cells with pleomorphic and irregularly-shaped nuclei, prominent nucleoli, and numerous mitotic figures. There is sharp demarcation of the epithelial nests of cells from the adjacent epidermal keratinocytes (1837). The overlying epidermis may be acanthotic. Both single tumour cells and nests of cells may involve the epidermis in a pagetoid fashion (1359). Keratinization is usually absent. Intercellular bridging between the tumour cells is inconspicuous. The tumour cells may contain glycogen (2000). Connection to the intradermal eccrine ducts may be observed. Deep dermal intralymphatic invasion may be observed in up to 15% of the lesions (1952).

The differential diagnosis includes eccrine poroma, hidroacanthoma simplex, and Paget disease (913). Eccrine poroma and hidroacanthoma simplex may show focal atypia, but the lesions are symmetrical and well circumscribed. Eccrine porocarcinoma may be differentiated from Paget disease by its relatively sparse epidermal involvement and greater dermal invasion, and the presence of glycogen rather than mucin in tumour cells (913). In the absence of residual eccrine poroma, it is very difficult to differentiate eccrine porocarcinoma from squamous cell carcinoma (1571).

Immunoprofile
The tumour nodules stain with antibodies to pan-cytokeratin; tumour cells may stain paler than adjacent epidermal keratinocytes (499,1072). Ductal structures within the tumour stain strongly positive with CEA and EMA (1359,2216).

Genetics
Mutation of the p53 gene with loss of its suppressor function has been widely noted with malignant transformation. P53 protein expression has been observed in both eccrine poromas and eccrine porocarcinoma (43,2327). P16 staining is uniformly negative (914).

Prognosis and predictive factors
Approximately 20% of eccrine porocarcinomas recur after excision (2216). Regional lymph node metastasis occurs in 20% of patients, while 12% develop distant metastases (2216). Patients with metastatic disease have a high mortality rate (170). Increased number of mitoses,
lymphovascular invasion and tumour depth greater than 7 mm have all been associated with a relatively poor prognosis (1952).

**Spiradenocarcinoma**

**Definition**
Spiradenocarcinoma is a malignant adnexal neoplasm resulting from malignant transformation of a benign spiradenoma.

**ICD-O code** 8403/3

**Histopathology**
In all cases there are recognizable areas of a benign spiradenoma with the usual well-defined dermal nodules composed of two cell types. Spiradenocarcinoma arising from benign spiradenoma presents two major histologic patterns (89, 725,884). In one type, there are areas showing gradual transition from benign to a malignant neoplasm. In these lesions the dual cell population of the benign neoplasm imperceptibly merges with the monomorphous cell population of the carcinoma. The usual structural pattern of spiradenoma disappears and is replaced by poorly defined cell nests and cords. Glandular and duct-like structures, as well as hyaline globules, are diminished or may be missing. These changes can be very focal in early lesions and can easily be missed without adequate tissue sampling. In the second type, the malignant changes are adjacent to the spiradenoma without structural or cytological transition. These neoplasms can present a wide spectrum of histologic features including squamous, Bowenoid, adenomatous, ductal carcino- ma-like, and even histioyte-like and carcinosarcomatous changes with rhabdomyoblastic or osteosarcomatous differentiation (1391,1548,1958). In advanced stages of both subtypes, necrosis, haemorrhage, and infiltrative growth can be observed.

**Immunoprofile**
Spiradenocarcinoma is positive for the majority of cytokeratins, CEA, EMA, and shows a spotty reaction for S-100 protein. Over-expression of P53 has also been reported (89,726,1555,2516).

**Synonym**
Malignant spiradenoma

**Epidemiology**
Spiradenocarcinoma is an extremely rare tumour. Approximately 50 well-documented cases have been reported. The tumour mainly affects middle age persons (mean age is 55 yr), and its incidence is similar in both sexes.

**Localization**
Spiradenocarcinoma can affect any body site, but the most common locations are the upper extremities, followed by the lower extremities, trunk, and the head and neck areas (725,884).

**Clinical features**
Typically there is a history of a long-standing lesion that suddenly became enlarged, ulcerated, tender, or changed its colour. The size of the tumour ranges from 0.8-10 cm. The mean duration of a pre-existent lesion is about 20 years before the diagnosis is made (725). The patient may also have multiple long-standing spiradenomas, which often coexist with cylindromas (89).
Histogenesis
Theoretically, spiradenocarcinoma can develop de novo. However, the tumour lacks distinctive microscopic features, therefore its histopathologic diagnosis requires recognition of a spiradenoma in association with the malignant changes.

Somatic genetics
TP53 mutations have been identified in carcinomatous portion of spiradenocarcinoma, whereas the spiradenoma part lacked mutations (239A).

Prognosis and predictive factors
Spiradenocarcinoma is an aggressive neoplasm with multiple local recurrences and eventual widespread metastases, resulting in death. The metastases most often involve lymph nodes, bones, and lungs. Management is primarily surgical; the role of radiation and chemotherapy is still to be defined (1110,1594).

Hidradenocarcinoma

Definition
Hidradenocarcinoma is the malignant counterpart of hidradenoma.

ICD-O code 8400/3

Synonyms
Clear-cell papillary carcinoma (1436), clear-cell hidradenocarcinoma (1249, 1470), malignant clear-cell hidradenoma (578,1237), malignant clear-cell acrospiroma (992), malignant eccrine acrospiroma (1741), primary mucocoeplidermoid hidradenocarcinoma (637), and malignant nodular clear-cell hidradenoma (204).

Epidemiology
Hidradenocarcinoma seems to be slightly more frequent in women than in men, with the mean age of 50 years, but cases have been also recorded in children (237,477).

Etiology
Most cases of this carcinoma arise de novo, but some cases are associated with a hidradenoma (237,1013,1237,1249,1427).

Localization
This carcinoma may appear in any area.

Clinical features
The neoplasm does not have any distinctive clinical features and usually presents as a slow growing solitary dermal or subcutaneous nodule.

Histopathology
Hidradenocarcinoma is composed of one or several tumour nodules, which vary in size and shape. Focal tubular and ductal structures may be present. Areas of necrosis en masse are common. Usually there is no connection between the epidermis and the tumour, but the surface epithelium may be ulcerated. The same cell types as seen in hidradenoma are found in hidradenocarcinoma. Atypical cells with pleomorphic nuclei and mitotic figures may be focally prominent, but some tumours lack nuclear atypia. Therefore, the diagnosis can be established only on the basis of architectural characteristics.

Immunoprofile
Neoplastic cells express low molecular weight cytokeratin CAM 5.2 and cytokeratin 19. CEA and EMA decorate the luminal border of ductal structures.

Histogenesis
Most neoplasms have apocrine differentiation, but some show eccrine features.

Prognosis and predictive factors
This carcinoma may metastasize widely and cause death. Of the 76 patients with this carcinoma described in the literature, 22 developed metastases (204,485,992,1013,1162,2468).
Mucinous carcinoma

Definition
Primary cutaneous mucinous carcinoma (MC) is a rare epithelial neoplasm occurring mostly, but not exclusively, in middle-aged and older patients. Although MC is characterized by destructive local growth and the potential of metastasizing to regional lymph nodes and even beyond them, it generally follows an indolent course with frequent local recurrences. Mucinous carcinoma metastatic to skin from another organ, particularly the breast and gastrointestinal tract, may be histologically indistinguishable from MC.

ICD-O code 8480/3

Synonyms
Primary cutaneous mucinous carcinoma. Colloid, gelatinous and adenocystic carcinoma.

Epidemiology
MC is very rare and occurs mostly between the fifth and seventh decades of life, with an age range between 8 and 84 years. MC is slightly more common in men than in women (1919).

Localization
Most MC arise on the head, favouring scalp and face with preference of the eyelids (199,305,1212,2217,2319). Rare sites are axillae, trunk, lower extremities, perianal area and vulva (1919).

Clinical features
MC presents as a solitary, slowly growing, painless nodular neoplasm. The tumour has a tan, grey, or reddish colour, a smooth surface, and a consistency ranging from soft to firm. Positive transillumination may be a helpful diagnostic tool.

Macroscopy
Grossly, most MC are well-circumscribed, un-encapsulated tumours in the dermis and the subcutaneous fat. Tumour diameters range between 1 and 8 centimetres, albeit larger variants have been reported (1231). On excision, the tumour appears fixed to the adjacent dermis and does not “shell out” (1919). The cut surface of excised specimens is gelatinous.

Histopathology
MC presents as an un-encapsulated asymmetric dermal tumour that may extend into the subcutis and even deeper tissue planes (1919). Tumour satellites may occur at some distance from the main tumour. MC is characterized by large pools of basophilic mucin, which are compartmentalized by delicate fibrous septa, thereby creating a honeycomb pattern. Within the lakes of mucin are small “floating” islands and bizarre clusters of neoplastic epithelial cells, sometimes exhibiting a cribriform arrangement. The epithelial component is denser at the periphery of the tumour. Small glandular or tubular structures containing mucin or showing signs of apocrine secretion occur only rarely. The small neoplastic cells are cuboidal, round, or oval with abundant cytoplasm that may be vacuolated. Nuclei are small with very little atypia. Mitoses are rare. The epithelial mucin is PAS-positive, hyaluronidase and sialinase labile, and consists of non-sulphated acid mucopolysaccharides with sialic acid.

Immunoprofile
Neoplastic cells express low molecular weight cytokeratins, CEA, EMA, GCDFP-15, alpha-lactalbumin, salivary amylase, beta-2-microglobulin. S100 expression is inconstant (199,404,664). Nuclear expression of oestrogen receptors may be strong, but the pattern of progesteron receptors is more variable (945). Cytokeratin 20 expression allows differentiation of mucinous gastrointestinal carcinoma metastatic to the skin from primary cytokeratin 20-negative cutaneous MC (664).

Variants
MC very rarely presents with focal neuroendocrine differentiation (1876), or with a growth pattern imitating infiltrating carcinoma of the breast (2557). Epidermotropism of neoplastic cells is unusual.

Electron microscopy
There are less well-differentiated inner pale cells and mucin-containing peripheral dark cells (990).

Differential diagnosis
Before a diagnosis of MC is established, a primary carcinoma in a breast or another organ (salivary and lacrimal glands, gastrointestinal tract, nose and...
paranasal sinuses, bronchi, ovary and renal pelvis) should be specifically sought and excluded as most cases of mucinous carcinoma in the skin are metastatic to it. Histological differentiation between primary cutaneous MC and metastatic mucinous carcinoma to the skin may be impossible, albeit the latter exhibits subtle histological variations (1919): e.g. larger clusters of cohesive neoplastic cells, less quantities of mucin, a striking predominance of epithelium over mucin, and the absence of delicate fibrous septa that intersect the lakes of mucin. Malignant mixed tumour of the skin exhibits tubular structures embedded in a myxoid, chondroid, or osteoid stroma, and distinctive polygonal and plasmacytoid neoplastic epithelia. The characteristic honeycomb pattern of MC is not present (1919).

**Histogenesis**
Histogenesis of MC has not yet been elucidated, but there is strong morphological evidence that MC may be apocrine in nature (1919).

**Prognosis and predictive factors**
In contrast to most other sweat gland carcinomas, MC is a low-grade malignant neoplasm with a tendency to persist at the original site but with a low metastatic potential. 10% of the MC so far reported metastasized to regional lymph nodes, but only 3% metastasized in a more widespread fashion (1830). While multiple recurrences, due to the existence of tumour satellites, are not unusual, death from MC is exceptional (1919).

**Digital papillary carcinoma**

**Definition**
Digital papillary carcinoma is regarded as an uncommon malignant adnexal neoplasm with potential for both recurrence and metastasis.

**ICD-O code**
8408/3

**Synonyms**
Aggressive digital papillary adenoma, digital papillary adenocarcinoma

Historically, this group of lesions was divided histologically into aggressive digital papillary adenomas and digital adenocarcinomas (1205). However, cases originally classified histologically as adenoma developed metastases, demonstrating that histologic parameters do not accurately predict behaviour or allow distinction between adenoma and adenocarcinoma (655). Therefore, the term aggressive digital papillary adenoma has been abandoned in favour of classification of all such lesions as digital papillary carcinoma.

**Epidemiology**
Digital papillary carcinomas present almost exclusively on the fingers, toes, palms, and soles. Hands are involved more frequently than feet. There is a male predilection, and most affected individuals are adults in the fifth and sixth decades of life.

**Clinical features**
Most cases present as a slowly growing deeply seated nodule on a digit. Lesions may be several centimetres in diameter. Pain is occasionally a presenting complaint, and may be related to tumour extension into underlying bone, joint, or nerve. Rarely, metastasis is the first manifestation of disease. Unless underlying bone has been invaded, routine roentgenographic examination may be essentially unremarkable.

**Histopathology**
Typically, tumours are composed of multi-nodular epithelial aggregates with cystic spaces in the dermis. A cribriform pattern of glands often fills the solid areas of tumour, while papillary epithelial projections are common within cystic spaces. The papillary projections are associated with fibrovascular cores in some areas, while in other areas papillae are formed by heaped up epithelium without stromal cores. The epithelium is composed of low columnar or cuboidal cells. Cytologic atypia is usually not marked. Mitoses and necrosis are frequent findings. Cysts contain either necrotic debris or eosinophilic secretory material. Some tumours are well-circumscribed, while others have an infiltrative growth pattern.

**Differential diagnosis**
The differential diagnosis includes papillary eccrine adenoma, which is usually well-circumscribed, and composed of dilated ducts with a distinct two cell layer and delicate papillae. Malignant adnexal neoplasms such as malignant acrosyringoma and malignant spiradenoma are also in the differential, but typically lack the pattern of papillary growth and/or back-to-back glands that characterize digital papillary carcinoma. In addition, malignant spiradenoma usually retains its characteristic two cell population (small basoloid cells and large pale peripheral cells) in at least some foci.

**Histogenesis**
The occurrence of digital papillary carcinoma on acral sites where eccrine
glands are abundant suggests an eccrine origin of this tumour. Although some cases show decapitation secretion, as is common in apocrine lesions, this phenomenon has also been observed in eccrine tumours. In addition, immunoreactivity for ferritin had led investigators to favour that digital papillary carcinomas derive from eccrine glands (417).

**Prognosis and predictive factors**

Complete surgical excision with negative margins is indicated, and sometimes requires amputation. Tumour recurrence is seen in up to 50% of patients, especially in cases without adequate primary excision (1205). Metastatic disease has been observed in 14% of cases (655). Metastases may accompany recurrent disease or occur without evidence of local recurrence. Lungs seem a favoured site for metastases, suggesting the probability of haematogenous spread of tumour. Tumour recurrence and metastasis does not seem to correlate with patient age, tumour size, or duration of tumour. Similarly, histologic features such as tumour differentiation, circumscription, or nuclear grade are not predictive of behaviour (655).

**Adenoid cystic carcinoma**

**Definition**

Primary cutaneous adenoid cystic carcinoma is a neoplasm of disputed histogenesis characterized by a cribriform pattern and frequent perineural involvement.

**ICD-O code** 8200/3

**Epidemiology**

Over 40 cases have been reported in the literature. Adenoid cystic carcinoma (ACC) affects middle-aged and older individuals (mean age: 58.1) and has a predilection for women (1219).

**Localization**

This neoplasm is most common on the scalp (35%) and chest and abdomen (24%) (446,1219).

**Clinical features**

Primary cutaneous adenoid cystic carcinoma has an indolent and progressive course. The average duration of the tumour prior to diagnosis is approximately 9.8 years (1219). The size of the tumour ranges from 0.5-8 cm, with an average size of 3.2 cm. Patients typically present with slowly expanding, firm, skin coloured nodules. Tenderness, ulceration and bleeding are variable and depend on the site of involvement. In the scalp region, alopecia may be an associated finding.

**Histopathology**

Primary cutaneous ACC is usually poorly circumscribed and is composed of islands, cords and strands of basaloid cells with a glandular, cystic, cribriform and tubular arrangement embedded in a loose fibrous and sometimes mucinous stroma. It typically occupies the mid and deep dermis and may extend into the subcutaneous fat (793). The epithelial cords have an infiltrative pattern and are not connected to the overlying epidermis. The tumour has a characteristic basophilic appearance on low power due to nuclear hyperchromatism and crowding. Nuclear palisading is absent. The tumour nests are surrounded by a prominent eosinophilic hyaline basement membrane-like material which is periodic acid-Schiff-positive, and diastase-resistant. The cystic spaces often contain abundant mucin (1812). The mucin is characteristically alcian blue (pH 2.5) positive. The epithelium consists of fairly uniform cells with darkly staining nuclei, which sometimes contain conspicuous, small, solitary nucleoli. Individual tumour cells have a scant amphophilic cytoplasm and an increased nuclear-cytoplasmic ratio. Mitotic activity is usually sparse with 1-2 division figures per high power field (x40) (2514). Perineural extension, a characteristic feature of salivary gland adenoid cystic carcinoma may be seen, however, not with the frequency seen in other organs. Before the diagnosis of a primary cutaneous ACC is made, the possibility of a
metastasis from other organs needs to be ruled out on clinico-pathological grounds. The adenoid cystic type of basal cell carcinoma is differentiated by the presence of palisading of the nuclei and stromal retraction.

Immunoprofile
Primary cutaneous adenoid cystic carcinoma stain positively for epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), broad-spectrum keratins, and low-molecular-weight keratins (CAM 5.2). Focal staining with S-100 and vimentin may be seen (210). Epithelial cells at the periphery of the tumour islands may express actin.

Histogenesis
The eccrine or apocrine origin of this tumour remains disputed. In the past, it has been regarded as an eccrine tumour, although some have been shown to arise from modified apocrine glands (2407).

Prognosis and predictive factors
An indolent but progressive course is the major characteristic of this tumour. The recurrence rate is high, ranging from 57-70% and therefore wide surgical excision extending well beyond the clinical confines of the tumour is recommended. Recurrences have been reported even with 2 cm margins and may occur many years after excision. For this reason some people favour Mohs micrographic surgery (462). Only 4 cases have metastasized to the lymph nodes and lungs.

Apocrine carcinoma

Definition
Apocrine carcinoma (AC) is a malignant sweat gland neoplasm with apocrine differentiation. Although an apocrine origin has also been postulated for adenoid cystic carcinoma, hidradenocarcinoma, spiradenocarcinoma, malignant cylindroma, and microcystic adnexal carcinoma, this remains unproven. These entities shall, therefore, be presented separately.

ICD-O code 8401/3

Synonyms
Apocrine adenocarcinoma, apocrine gland carcinoma

Epidemiology
AC is a rare tumour. Both genders are almost equally affected, and there appears to be no racial predilection (1785,2460).

Etiology
The etiology of AC is unknown. The fact that all patients were over 25 years (824) suggests that full maturity of the apocrine glands is a prerequisite.

Localization
Most AC arise in the axilla and, to a lesser extent, in the anogenital region. Rare locations include the scalp, face, chest, and distal upper extremities (536,988, 1785,2055,2460). Peculiar variants have been described on the ear (ceruminous gland carcinoma) and the eyelid (Moll gland carcinoma) (2139,2172).

Clinical features
Because reports are sporadic and may have included a proportion of benign lesions it is difficult to establish a precise clinical profile for AC. Apparently, there are no distinctive features that might enable a confident clinical diagnosis of AC. Most tumours are solitary, but a patient with bilateral axillary AC has been reported. AC presents as single or multiple, firm or cystic nodules with a reddish or purplish hue of the overlying skin, sizing between 1.5 and 8 cm (2460). Ulceration and haemorrhage may be present. The patients’ age at presentation ranges from 25 to 91 years, with an average age of 57.9 years (2460). In many cases, the lesions had been standing for more than 10 years, and even up to 30 years before diagnosis (1650). Some tumours have arisen within a nae- vus sebaceous (644).

Histopathology
AC is typically centred on the deeper dermis and tends to spread into the subcutaneous fatty tissue (1785,2460). Extension into the epidermis also occurs, occasionally in the form of extramammary Paget disease (1647). The tumours are usually poorly circumscribed with infiltrating borders. Neighbouring apocrine glands occasionally show in situ carcinoma (988,2460). The growth patterns of AC are highly variable, including tubular,

![Fig. 3.17 Apocrine carcinoma. A Well differentiated cutaneous apocrine carcinoma. Glandular structures with tubulopapillary growth pattern and apical decapitation secretion. B Poorly differentiated cutaneous apocrine carcinoma. Micronodular and trabecular growth pattern with hardly any gland formation, hyaline stroma. The cells have scanty amphophilic cytoplasm and contain vesicular nuclei with prominent nucleoli and occasional mitotic figures.](image_url)
Appendageal tumours

Differential diagnosis
The main differential diagnosis is with (tubular) apocrine adenoma, and the histologic features that distinguish these conditions are often subtle. Whilst vascular and neural invasion are diagnostic of carcinoma, stromal invasion is less so and may be difficult to ascertain. Tumour silhouette, cellular pleomorphism and mitotic activity may provide clues to malignancy. As focal squamous differentiation may occur in AC (1785) anaplastic squamous cell carcinoma may have to be considered in the diagnostic differential.

AC is otherwise indistinguishable from apocrine mammary carcinoma metastat-
ic to the skin or apocrine carcinomas arising in ectopic breast tissue in the axilla. Therefore, the diagnosis of primary cutaneous AC rests on a meticulous clinicopathologic correlation.

Immunoprofile
The cells of AC express low molecular weight cytokeratin (CAM5.2), epithelial membrane antigen, carcinoembryonic antigen, cytokeratin15, gross cystic disease fluid protein (GCDFP)-15 (1785) and occasionally S-100 protein (1343, 1785). Myoepithelial cells, detectable by SMA or CK 5/6 immunostaining, are typically absent (988,2460).

Histogenesis
AC is thought to arise from preexisting apocrine (sweat) glands (988,1785,2139, 2459). An interesting alternative origin are the newly described mammary-like sweat glands of the anogenital region, which may also give rise to eccrine tumours (2408).

Prognosis and predictive factors
The majority of AC are slow growing tumours with a tendency toward a prolonged course. The overall mortality is low, despite frequent recurrences (30%) and metastases to regional lymph nodes (50%) (536,1785,2460). Wide dissemination and tumour-related deaths have nevertheless been described (437,1785, 2172,2460). As distant metastases may be a late event in the course of AC a prolonged follow-up is advisable. Reliable predictive factors have not been established.

Paget disease and extramammary Paget disease

Definition
Paget disease of the breast and extramammary Paget disease are intraepidermal adenocarcinomas characterized by large atypical and pale staining cells scattered throughout the epidermis either as single cells or in small clusters. Mammary Paget disease (MPD) resembles an eczematous eruption of the nipple and areola, and in almost all cases constitutes skin involvement by an underlying in situ or invasive ductal carcinoma of the breast.

Extramammary Paget disease (EMP) is a scaly erythematous eruption affecting apocrine gland bearing areas of the skin, mainly the female and male genital areas. The majority of cases represent an apocrine adenocarcinoma in situ that has a high recurrence rate and may invade the dermis and then possesses metastatic potential. In a subset of cases EMP is the skin manifestation of an underlying internal malignancy. The skin manifestations of these cases are clinically and histologically indistinguishable from cases not associated with internal malignancy.

ICD-O codes
Paget disease of breast 8540/3
Extramammary Paget disease 8542/3

Historical annotation
In 1874 Sir James Paget first described “about fifteen cases” of a chronic eczematous eruption of the nipple and areola and noted that mammary cancer developed in all patients within two years (1766). George Thin described the histopathologic features of this condition in 1881. The term Paget disease was coined in 1889 by Radcliffe Crocker when he described a morphologically and histologically similar eruption affecting the penis and scrotum (561).

Epidemiology
MPD occurs almost exclusively in women. Exceptional cases of men with MPD have been reported (927). One to two percent of female patients with breast carcinoma develop Paget disease (1971). Ten to 28% of cases of Paget dis-
ease are detected only on histologic examination of the nipple in a mastectomy specimen, without a clinically apparent lesion (1971). No accurate epidemiologic data is available for EMP. It is a rare condition that comprises less than 2% of primary neoplasms of the vulva. EMP occurring in sites other than the vulva is even less common. In genital EMP, women are more commonly affected than men. Most patients are above the age of 60.

Etiology
MPD is almost always associated with an underlying carcinoma of the breast, and the etiology is the same as for breast carcinoma. The inciting factors for primary EMP are unknown. Secondary EMP is an expression of an underlying internal malignancy and the etiology parallels that of the underlying tumour.

Localization
MPD involves the nipple and areola and in advanced cases may extend to the adjacent skin. EMP involves apocrine gland bearing areas and is most common in the genital area, groin, perineum or perianal region. Axillae, eyelids and external auditory canals rarely may be involved.

Clinical features
Patients who present with MPD initially develop erythema of the nipple and areola. The lesion then progresses to scaly, crusted thick plaques and ultimately to areas of erosion and ulceration. Patches and plaques are almost always unilateral and sharply circumscribed, and sometimes pruritic or painful. In approximately half of the cases a breast mass is palpable. Nipple retraction and serosanguinous discharge may be features of advanced cases with a large underlying carcinoma. Not all patients with MPD have clinical symptoms; 10-28% of cases are detected only on histologic examination in a mastectomy specimen (1971). The differential diagnosis includes squamous cell carcinoma in situ and eczema. Once a diagnosis of MPD is established the patient needs to be evaluated with imaging studies and other procedures for breast carcinoma. If MPD is associated with a palpable tumour mass, the underlying carcinoma will be invasive in more than 90% of cases. If no tumour mass can be detected clinically, less than 40% of women will have invasive carcinoma. Patients with EMP most commonly present with pruritus or burning. The skin shows well-demarcated erythematous scaly patches and plaques, which may be ulcerated. Following a diagnosis of EMP the patient needs to undergo thorough examination to rule out an associated internal malignancy.

Tumour spread and staging
MPD without invasive carcinoma on histologic examination is classified as carcinoma in situ (Tis). MPD with a contiguous or non-contiguous invasive component on histology is staged according to the invasive component using the guidelines for staging of breast carcinoma. Primary EMP is staged either according to the FIGO (Fédération Internationale de Gynécologie et d’Obstétrique) or the TNM system of the AJCC (American Joint Committee on Cancer) for vulvar tumours. After a long period of in situ growth EMP can eventually invade the dermis and acquire metastatic potential. Typically, invasive carcinoma associated with EMP first spreads to locoregional lymph nodes and ultimately may develop distant metastases. Secondary EMP is staged according to the criteria for the associated internal malignancy.

Histopathology
On histologic examination MPD and EMP are characterized by neoplastic cells with large nuclei, prominent nucleoli and abundant pale to amphophilic cytoplasm that are scattered throughout the entire epidermal thickness. These cells occur singly and in clusters and often are more numerous in the basal layers of the epidermis. Acinus formation may be present. Paget cells can contain cytoplasmic melanin pigment, a feature that should
not imply melanocytic differentiation. The epidermis is often hyperkeratotic and acanthotic, especially if the disease has been chronic. Particularly in EMP, the tumour cells have a propensity to track along skin appendages. A dermal perivascular lymphohistiocytic infiltrate accompanies the epidermal changes. Paget cells are positive with conventional mucin histochemistry in 40–70% of cases (1297). In MPD the associated in situ or invasive breast carcinoma is of ductal differentiation in the majority of cases. Lobular carcinoma only rarely gives rise to MPD. Histologically, EMP without an internal malignancy cannot be differentiated from those cases with associated neoplasm. The histopathologic differential diagnosis includes pagetoid squamous cell carcinoma in situ, superficial spreading malignant melanoma, pagetoid Spitz naevus, clear cells of Toker, pagetoid dyskeratosis, clear cell papulosis, sebaceous carcinoma, intraepidermal Merkel cell carcinoma, eccrine porocarcinoma, cutaneous T-cell lymphoma, Langerhans cell histiocytosis and epidermotropic metastasis.

Immunoprofile
The immunophenotype of MPD closely matches that of the underlying breast carcinoma (511). Paget cells are practically always positive for low molecular weight cytokeratins (detectable by specific or broad spectrum cytokeratins such as CK7, CAM5.2 and AE1/AE3) and epithelial membrane antigen (EMA), variably positive for polyclonal carinoembryonic antigen (pCEA) and lack lymphoid markers such as leukocyte common antigen (LCA) and CD3 (1036,1461). Gross cystic disease fluid protein-15 (GCDFP-15) has been reported in approximately 50% of cases, similar to that of breast carcinoma in general (511). As in breast carcinoma, reports of S100 reactivity are quite variable, ranging from 0-26% (1757,2548). Approximately 5% of Paget cases are oestrogen receptor (ER) and/or progesterone receptor (PR) positive (511).

The tumour cells in primary and secondary EMP are positive for simple cytokeratins (CAM5.2, AE1/AE3), EMA and CEA (1004,1539,1757,2548). Immunohistochemistry can also suggest the presence of an associated internal malignancy, because primary EMP has the staining characteristics of an apocrine carcinoma and is almost always CK7 positive and gross-cystic disease fluid protein (GCDFP) positive, while CK20 is commonly negative whereas the opposite is true for EMP with associated internal malignancy. The cells in these latter cases are also mostly CK7 positive, but more often express CK20 and do not stain for GCDFP (851,852,1298,1461). In EMP positive staining with CK20 and lack of staining with GCDFP should prompt an even more thorough evaluation for underlying malignancy.

The most useful keratin markers for MPD and EMP are CAM5.2 and CK7 because they stain >90% of Paget cells but do not react with epidermal or mucosal keratinocytes, a characteristic that makes both antibodies very useful in the evaluation of surgical margins and invasion.

Histogenesis
MPD is almost always associated with an underlying carcinoma of the breast either in situ or invasive. MPD represents the retrograde extension of an underlying carcinoma into the epidermis, either in a contiguous fashion, through spread along the lactiferous ducts or through intraepidermal metastasis. Cases without underlying carcinoma exist but are exceptional (1159). The etiology of these cases is speculative, but probably they are analogous to primary EMP, representing apocrine adenocarcinomas in situ, derived from Toker cells. Toker cells are cells with bland cytologic features and clear cytoplasm that have been identified by standard light microscopic means in ~10% of normal nipples (1461). They are derived from lactiferous duct lining cells and preferentially cluster in the epidermis near lactiferous duct ostia. Primary EMP is an apocrine adenocarcinoma in situ that most likely arises from intraepidermal cells of apocrine gland ducts. These cells, analogous to Toker cells of the nipple, have been recently demonstrated in the epidermis of vulvectomy specimens in association with mammary-like glands (2531). In secondary EMP the disease represents migration of an underlying internal malignancy to the epidermis. Tumours associated with EMP include rectal adenocarcinoma, transitional cell carcinoma of the urethra and bladder, carcinoma of the Bartholins glands, prostate carcinoma, cutaneous adnexal carcinoma and carcinoma of the vagina and cervix.

Prognosis and predictive factors
The prognosis of MPD depends on the size and characteristics of the underlying breast carcinoma. Patients with MPD but without a clinically detectable breast mass have a much better prognosis. In a recent study, 61 patients with MPD and without palpable mass were treated with a cone excision of the nipple-areola complex and radiation therapy. Histologic examination revealed underlying DCIS in 93.3% of patients and Paget disease, only, in 7%. The recurrence rate at a median follow up of 6.4 years was 5.2% (1 patient with DCIS and 3 patients with invasive carcinoma) (242). The majority of cases of EMP are not associated with another neoplasm and show a recurrence rate of approximately 30% after surgery, but do not metastasize. Around 10% of patients will develop invasive adenocarcinoma that may progress to metastatic disease (710). The rate of an associated internal malignancy varies from 15% to 33% and is more common in perianal EMP than vulvar EMP (1024). In these cases the associated tumour drives the clinical behaviour, treatment and prognosis.
Hidrocystoma

**Definition**
Hidrocystomas are cystic proliferations of the sweat glands. They have either apocrine or eccrine differentiation, with the majority being of apocrine nature. Apocrine hidrocystomas are cystic adenomas that arise from the apocrine secretory coil, while eccrine hidrocystomas represent retention cysts of the eccrine cyst duct (607,1919,2047,2188).

**ICD-O code** 8404/0

**Synonyms**
Several and sometimes confusing terms have been used to designate hidrocystomas, to wit: apocrine gland cyst, papillary apocrine gland cyst (1919), apocrine cystadenoma (1568).

**Epidemiology**
Hidrocystomas are relatively rare and account for approximately one per thousand of submitted cutaneous biopsies (607). They normally present as solitary lesions, however patients with multiple lesions have been observed. Hidrocystomas usually affect middle-aged or older individuals although rare examples have been described in children and adolescents; both sexes are equally affected.

**Localization**
Hidrocystomas have a predilection for the face and neck, mainly the periorbital area, but may also affect other parts of the body such as the perineum.

**Clinical features**
Hidrocystomas present as dome-shaped, cystic firm papules or nodules, with a slightly blue colouration. In some cases the content of the cyst is brown or black.

**Etiology**
The exact cause of hidrocystomas is not known. They have been reported to be exacerbated with high temperatures and to completely disappear with cold weather and atropine therapy (2236). There is an increased incidence of hidrocystomas in hyperthyroid patients, perhaps related to hyperhidrosis (1270,1673).

**Macroscopy**
The lesions are of variable size ranging from 0.5-1.0 cm, although lesions of up to 7.0 cm have been reported. Hidrocystomas are usually located in the dermis, but in some cases they may be present in the subcutaneous fat. The cut surface reveals a well-circumscribed, unilocular or multilocular cyst.

**Histopathology**
Hidrocystomas can be uni or multilocular and are usually lined by a double layer of epithelium. The inner layer contains large columnar cells with eosinophilic cytoplasm which has luminal decapitation secretion, while the outer layer is flat and composed of myoepithelial cells. The term “papillary apocrine gland cyst” has been applied for hidrocystomas with papillary projections of epithelium into the lumen (1919). Occasionally, hidrocystomas may show a single cystic cavity lined by one or two layers of flattened epithelium as a consequence of the pressure exerted by the contents of the cyst. In this circumstance, distinction from eccrine hidrocystomas, which have a similar lining, becomes impossible (671).

![Fig. 3.22 Hidrocystoma presenting as small, dome-shaped lesion on the right side of the face, containing a clear fluid.](image)

![Fig. 3.23 Hidrocystoma, papillary cystadenoma. A Example of the so-called "papillary apocrine gland cyst". These lesions are characterized by the presence of papillary projections of epithelium into the lumen. B The papillary projections contain a core of connective tissue and are lined by cuboidal epithelium. C This picture depicts a typical example of an apocrine hidrocystoma. The lesion is cystic and lined by a cuboidal epithelium. D At higher magnification the cyst is lined by a double layer of cuboidal cells with evidence of decapitation and secretion.](image)
Hidrocystomas express epithelial membrane antigen (EMA) and lysozyme in the cells of the cyst wall; carcinoembryonic antigen (CEA) decorates the luminal cells \(^{1217}\). The pattern of cytokeratin expression is variable \(^{607,17444}\); there is expression of cytokeratins 7,8,18,19 in the luminal cell layer and cytokeratins 1,5,10,14 in the basal and luminal cell layers.

Smooth muscle actin (SMA) is present in the basal layer \(^{607}\). Human milk fat globulin 1 (HMFG) is expressed by the apocrine sweat gland only \(^{607}\). S-100 protein is positive in the secretory portion of normal eccrine glands and in the myoepithelial cells of apocrine glands \(^{1678,2358}\).

**Prognosis and predictive factors**

Complete excision is usually curative. Topical atropine or scopolamine has also been used \(^{56,503,2236}\). Avoidance of a hot environment or other factors that increase perspiration lessens the severity of these lesions \(^{1668}\).

**Syringoma**

**Definition**

Syringomas are small benign adnexal neoplasms that are almost always multiple. They are composed of sweat gland epithelium (presumably eccrine) within densely sclerotic stroma.

**ICD-O code** 8407/0

**Synonyms**

Eccrine syringoma, lymphangioma tuberosum multiplex.

**Epidemiology**

Syringomas are common lesions, found more often in women than men. They appear more commonly in Asians than in other races. Syringomas usually arise in adolescence or early adulthood, but are most often biopsied in the 4th decade. Most are sporadic, though some eruptive and disseminated forms may be familial. Syringomas appear to be more common in Down syndrome. A clear cell variant has been associated with diabetes mellitus in many instances \(^{800,2474}\).

**Localization**

By far, the most common sites of involvement are the lower eyelids. Involvement of the upper cheeks is not uncommon. Unusual sites of involvement include the neck, chest, axillae, pubic area, periumbilical region, penis, vulva, hands and forehead. Unilateral linear lesions have been described \(^{552}\). Eruptive syringomas are typically numerous, widespread and may appear in crops \(^{1388}\).

**Clinical features**

The lesions are numerous, firm, smooth, dome-shaped, skin coloured or slightly yellowish papules, 1-3 mm in diameter, usually situated in skin of the lower eyelids. Syringomas are rarely solitary.

**Histopathology**

Syringomas are small lesions, restricted to the upper reticular dermis. They are composed of numerous small solid nests, cords and tubules of epithelial cells within a dense struma of compactly arranged bundles of collagen, accompanied by relatively few fibrocytes. The epithelial aggregates are usually evenly distributed throughout the lesion. The epithelial cells of syringoma show small nuclei, inconspicuous nucleoli and absent mitotic figures. Cytoplasm ranges from eosinophilic to clear. The epithelial cells within tubular structures show an inner layer of luminal cells and one or two rows of more peripheral cells. Tubular lumina may be distended, causing flattening of the inner most lining cells. Larger aggregates of cords and nests of cells may exhibit a “comma-like” or “tadpole-like” configuration. The cords, nests and tubules of syringomas branch and anastomose. Milia may be present, and these may rupture producing granulomatous inflammation and subsequent calcification. Syringomas may become confluent. Eruptive syringomas are similar to standard syringomas; however, the stromal component is sometimes less prominent.

In most conventional syringomas some epithelial cells have pale cytoplasm. In some lesions, these cells predominate, and this pattern has been termed “clear-cell syringoma”; it has frequently been associated with diabetes mellitus, but it may be seen sporadically.

**Differential diagnosis**

Desmoplastic trichoepitheliomas differ from syringomas by being larger, deeper, and composed of epithelial elements that show follicular differentiation. Superficial biopsies of microcystic adnexal carcinoma may greatly resemble syringoma. Microcystic adnexal carcinomas are larger, asymmetric and less circumscribed than syringoma. Virtually all microcystic adnexal carcinomas extend into subcutaneous fat or skeletal muscle, whereas syringomas are restricted to the upper two thirds of the reticular dermis.
Prognosis
Syringomas are benign. Association with or progression towards carcinoma has not been described.

Poroma

Definition
Poromas are benign adnexal neoplasms with terminal ductal differentiation. Although historically considered a neoplasm of eccrine differentiation, poromas can show either eccrine or apocrine lineage.

ICD-O code 8409/0

Synonyms
Eccrine poroma, hidroacanthoma simplex, dermal duct tumour, syringoacanthoma

Epidemiology
Poromas usually present as solitary tumours on acral sites, although they can be seen in virtually any cutaneous location. Most poromas arise in middle age with no sex predilection. Uncommonly, multiple poromas are seen, either limited to palms and soles or in a widespread distribution, for which the term poromatosis has been applied.

Clinical features
Poromas typically manifest as dome-shaped cutaneous papules, nodules or plaques, generally measuring less than 1 cm in diameter. Some lesions are highly vascular and may show a tendency to bleed, particularly on acral sites. Uncommonly, poromas are pigmented. Rapid growth has been reported during pregnancy (920). Multiple poromas have developed after electron beam therapy for mycosis fungoides (1348) and occurrence in areas of chronic radiation dermatitis has been reported (1802). Occurrence of poroma within a naevus sebaceous has been documented (1133).

Histopathology
Poromas are well-circumscribed tumours composed of a proliferation of uniform basaloid, cuboidal cells punctuated by focal ducts and occasional cysts. The epithelial cells of poromas typically extend from the lower epidermis into the dermis in broad columns. The epithelium of poromas is sharply demarcated from adjacent keratinocytes. Nuclei are small and regular, and cytoplasm is modest in amount. The cytoplasm often contains glycogen. Most poromas contain ductal structures lined by PAS positive diastase-resistant cuticles. Small areas of necrosis as well as mitoses are seen in otherwise banal poromas, and are of no prognostic significance. Foci of sebaceous differentiation may be observed. The stroma surrounding poromas is often richly vascular, and may contain granulation tissue. Architecturally, poromas show a spectrum of change from predominately intraepidermal lesions (hidroacanthoma simplex) to primarily dermal-based neoplasms (dermal duct tumour). Another rare variant has been termed syringoacanthoma, representing a clonal pattern of poroma within an acanthotic epidermis with prominent surface keratinization.

Differential diagnosis
Histologically the differential diagnosis includes seborrheic keratosis, which typically shows keratinization with horn cysts, a more sharply demarcated lower border, and absence of ductal structures. Basal cell carcinoma may sometimes be considered histologically, but shows more obvious peripheral palisading, nuclear variability, and little or no glycogen.

Histogenesis
Poromas may show evidence of either eccrine or apocrine differentiation (970). Immunohistochemical studies reveal that poroma cells express a cytokeratin phenotype similar to basal cells of the eccrine ducts in some cases (2466). The absence of myoepithelial cells also suggests differentiation toward the excretory (ductal) component of sweat glands. Occurrence of poromas within folliculo-sebaceous lesions such as naevus sebaceous, and presence of sebocytes within poroma, implicates origin from apocrine glands in some cases (662, 970).

Genetics
Some cases of poromatosis have been
associated with hidrotic ectodermal dysplasia (2519). Rare cases of poroma have occurred in the setting of naevoid basal cell carcinoma syndrome (904). Studies of p53 protein have shown high expression in some poromas as well as in some porocarcinomas, but staining is not correlated with duration of tumours (43). Therefore, while p53 mutation may be involved in progression of some poromas to porocarcinoma, other oncogenes or factors are also likely play a role in malignant transformation of poromas.

Prognosis
Poromas are benign and simple excision is curative.

**Syringofibroadenoma**

**Definition**
Syringofibroadenoma is a rare benign eccrine tumour with anastomosing strands and fibrovascular stroma, first described by Mascaro (1529). Multiple lesions of syringofibroadenoma are referred to as eccrine syringofibroadenomatosis (456,2189).

**ICD-O code**
8392/0

**Synonyms**
Eccrine syringofibroadenoma (663), eccrine syringofibroadenomatous hyperplasia (1721), eccrine syringofibroadenomatosis (456,2189), acrosyringeal adenomatosis (950).

**Epidemiology**
Syringofibroadenoma is rare, with about 75 reported cases. It occurs primarily in older adults.

**Localization**
Most of syringofibroadenomas arise on acral areas (498,685,769,2248,2313, 2344,2399).

**Clinical features**
The most common clinical presentation is solitary, often verrucous papules or nodules (1529,2248,2313). Unusual presentations include large plaques, linear lesions, and disseminated tumours (1259,2189,2248).

**Etiology**
Occasionally, syringofibroadenoma can be associated with other entities, both inflammatory and neoplastic, including bullous pemphigoid (1720,1721), lichen planus (780), ulcers (1092,2399), squamous cell carcinoma (1399), sebaceous naevus (1719), and chronic lymphoedema (806). Based on the latter association and the presence of fibrous stroma, some authors consider syringofibroadenoma as a hyperplasia rather than a neoplasia (779,780,806,1092,1399,1719, 1720). It may be associated with Schöpf-Schultze-Passarge syndrome (2189), an autosomal dominant syndrome with palmoplantar keratoderma, hypodontia, and eyelid hidrocystomas, whose genetic aberration has been localized to chromosome 13q (1259).

**Histopathology**
Syringofibroadenoma is characterized by multiple anastomosing cords and strands of monomorphic cuboidal cells (26,1529). The epithelial cords extend usually into the mid-dermis, and are embedded in a loose fibrovascular stroma. Rarely, a clear cell variant has been observed (781,2415).

**Immunoprofile**
Light microscopy usually leads to a specific diagnosis. The tumour cells are usually positive for both keratin 6 and 19 as well as filaggrin (1108,1304,1742,1745, 2314).

**Prognosis and predictive factors**
Syringofibroadenoma is a benign condition, and solitary lesions are cured by complete excision, while the treatment of multiple lesions is dependent on the size and location. Cases of syringofibroadenoma with foci of atypical squamous cells have also been described (255, 1215).
**Hidradenoma**

**Definition**
Hidradenoma is a benign adnexal neoplasm, closely related to poroma, that displays a limited degree of ductal differentiation. While historically considered eccrine, recent evidence suggests that hidradenoma can be either apocrine or eccrine (825,1543).

**ICD-O code**
8402/0

**Synonyms**
Clear cell hidradenoma, nodular hidradenoma, poroid hidradenoma, acrospiroma, solid-cystic hidradenoma (825,980,1374).

**Epidemiology**
Hidradenomas are sporadic with no sex predilection. Most develop in adults, but childhood onset has been documented (715,1652). Hidradenoma can also arise as a secondary neoplasm with naevoid sebaceous.

**Localization**
Hidradenomas commonly develop on the scalp, trunk, and proximal extremities, and rarely on the hands and feet. Eyelid lesions have also been noted (911).

**Clinical features**
Hidradenomas lack any distinctive clinical features, presenting as skin-coloured to red-brown nodules.

**Histopathology**
Hidradenoma is a mostly dermal neoplasm with a nodular, circumscribed pattern at scanning magnification. Sometimes an epidermal attachment can be identified. The intervening stroma is often sclerotic and may be highly vascularized, with ectatic vascular channels. Hidradenoma is composed of several types of cells: Clear or pale cells, which contain abundant glycogen, and show distinct cell membranes (578). The number of clear cells varies from lesion to lesion. When these cells predominate, the name clear-cell hidradenoma is appropriate (2544). Squamoid cells are polygonal with a central vesicular nucleus and eosinophilic cytoplasm, and often are arranged in whorls (1774). Mucinous cells are the least common component. They are large cells with fine basophilic granular cytoplasm. Cuboidal or columnar cells line the tubules and show evidence of apocrine differentiation (1427). Transition between different types of cells is frequent. The cells are arranged in sheets, punctuated by ducts and glandular areas which may show apocrine differentiation. Hybrid lesions including compact poroid cells with prominent ductal differentiation have been referred to as poroid hidradenomas.

**Prognosis**
Complete excision is curative.

**Spiradenoma**

**Definition**
Spiradenoma is a benign dermal neoplasm that can show either eccrine or apocrine differentiation, and significant morphologic overlap with cylindroma.

**Historical annotation**
Chandeluz, in 1882, probably first described this tumour (765). Unna first coined the term spiradenoma. In 1956 Kersting and Helwig published the classic paper on spiradenoma in 136 patients (1250). Additional series of spiradenoma have since been published (12,1496).

**ICD-O code**
8403/0

**Localization**
Most spiradenomas appear on the face...
Appendageal tumours and upper trunk, but they can also affect other sites.

**Clinical features**

Usually, spiradenoma appears as a solitary, well-circumscribed, firm nodule, measuring usually less than 1 cm, but giant variants and multiple lesions have also been described. Unusual cases show multiple spiradenomas arranged in a zosteriform linear pattern. Spiradenoma appears in adult life, although there are also reports of congenital cases, and in one patient spiradenoma developed within a naevus sebaceous of Jadassohn. Pain is one of the main clinical characteristics of spiradenoma. The mechanism of pain or tenderness in spiradenoma is not clear.

**Histopathology**

At low power magnification, spiradenoma appears as a solid neoplasm composed of a single or few nodules of basaloid cells. These aggregations are round with smooth borders and involve the full thickness of the dermis, sometimes extending into the subcutaneous fat. Often, the intervening stroma is oedematous with ectatic vessels. Dilated vessels rimmed by sclerosis have been interpreted as “ancient” changes due to long-standing lesions. Another characteristic finding is the presence of abundant lymphocytes scattered within the tumour nodules. At higher magnification, two distinct populations of neoplastic epithelial cells can be seen, dark and pale. Dark cells are small, basaloid cells with hyperchromatic nuclei located at the periphery, whereas pale cells, which are larger with vesicular nuclei and ample pale cytoplasm, tend to be near the centre of the clusters. Tubules lined by two rows of epithelial cells may be found within the tumour nodules. A characteristic feature is the presence of eosinophilic PAS positive globules throughout the entire neoplasm, sometimes surrounded by neoplastic cells in pseudorosette fashion. These globules are composed of basement membrane material. Sometimes the stroma shows striking oedema. Spiradenoma in children may show a different histopathologic pattern. The neoplastic cells appear more immature, making the distinction between clear and dark neoplastic epithelial cells difficult, and the neoplasm may be misinterpreted as a mesenchymal neoplasm. The frequent association of spiradenoma and cylindroma, a likely apocrine neoplasm, and the sporadic association of spiradenoma with neoplasms with follicular differentiation such as trichoepithelioma, support the notion that spiradenoma and cylindroma are closely related, probably representing two morphologic expressions of the same basic neoplastic process.

**Immunoprofile**

The tumour cells express cytokeratins, and the tubular structures are CEA positive. Inflammatory cells scattered within the neoplastic aggregations have been identified as abundant T lymphocytes and Langerhans cells.

**Histogenesis**

The histochemical and immunohistochemical studies have not clarified the histogenesis of spiradenoma. The frequent association of spiradenoma and cylindroma, a likely apocrine neoplasm, and the sporadic association of spiradenoma with neoplasms with follicular differentiation such as trichoepithelioma, support an apocrine line of differentiation for spiradenoma on the basis of the common embryologic origin for the three elements of the folliculo-sebaceous-apocrine unit. This is furthermore supported by some examples of spiradenoma that show decapitation secretion in the cells lining the luminal border of the tubular structures. Therefore, the qualifying term of “eccrine” that almost invariably is applied to spiradenoma is inaccurate.

**Prognosis and predictive factors**

Spiradenoma is a benign neoplasm. Because of the sharp demarcation of the tumour from the surrounding stroma, excision is easily accomplished. Several examples of carcinomas arising in long-standing spiradenomas have been described. In those instances, enlargement of a nodule that had been stable for many years seems to be the sign of malignant transformation. It appears to be accompanied by increased expression of p53 protein.
**Cylindroma**

**Definition**
Cylindroma is a relatively undifferentiated benign adnexal neoplasm with a mosaic microscopical pattern. Cylindroma commonly occurs as a hybrid with spiradenoma, an event that has been referred to as cylindrospiradenoma or spiradeno-cylindroma (301,846,1543,1600).

**ICD-O code**
8200/0

**Synonyms**
Cylindrospiradenoma (301), spiradenocylindroma (1600)

**Epidemiology**
Cylindromas may be solitary or multiple, arising on a sporadic basis or as part of Brooke-Spiegler syndrome. There is no sex predilection.

**Etiology**
The etiology is unknown. A link to chromosome 9 seems likely for multiple spiradenomas and cylindromas in the context of the Brooke-Spiegler syndrome, as the gene has been mapped to 9p21 (951,1538).

**Localization**
The vast majority of cylindromas occur on the scalp or face, especially in the vicinity of the ear. Uncommonly, cylindromas develop on the trunk or proximal extremity.

**Clinical features**
Cylindromas are typically smooth, dome-shaped hairless red-brown papules and nodules. Extensive scalp involvement can create clinical morphology resembling a headpiece (“turban tumour”).

**Histopathology**
Cylindroma is a mostly dermal and sometimes subcutaneous neoplasm with a multinodular, circumscribed pattern at scanning magnification. Individual nodules are composed of mosaic nests of undifferentiated basaloid cells with small darkly-staining nuclei and scant cytoplasm; individual nests fit tightly and neatly within larger nodules in a pattern that has been likened to that of a jigsaw puzzle. The nests of cylindroma are commonly surrounded by a rim of densely eosinophilic PAS-positive basement membrane material, and the nests are also punctuated by small round “droplets” with similar staining qualities. Hybrid lesions with areas of cylindroma and spiradenoma in juxtaposition are not uncommon (301,846,1543,1600).

**Immunoprofile and histogenesis**
Refer to the previous chapter on spiradenoma.

**Prognosis and predictive factors**
Simple excision is usually curative. Malignant transformation is extremely uncommon.

**Tubular and tubular papillary adenoma**

**Definition**
Tubular apocrine adenoma is a benign dermal adnexal neoplasm demonstrating apocrine differentiation that typically occurs in a broad age group of women on the scalp region.

**ICD-O code**
Tubular adenoma 8211/0
Tubular papillary adenoma 8263/0

**Synonyms**
Apocrine adenoma, tubular adenoma, tubulopapillary hidradenoma, papillary tubular adenoma

**Epidemiology**
Tubular apocrine adenomas occur sporadically with a female predilection (1361). A broad age group may be affected (1361). Some neoplasms may occur in association with a syringocystadenoma papilliferum (76,489,1111,2364) and can also arise within an organoid naevus (1111,1361,2394).

**Localization**
Tubular apocrine adenomas commonly occur on the scalp and less often at other sites including the leg, trunk, axillary and anogenital areas (1361).

**Clinical features**
Tubular apocrine adenomas present as asymptomatic solitary nodules that are skin-coloured to pink-red in appearance with either a smooth or irregular appearance (1361). Most tumours range in overall dimension between 1 to 2 cm but rarely may be as large as 7 cm (1361).

**Histopathology**
Tubular apocrine adenomas are well-circumscribed dermal neoplasms that may extend into the subcutis. They have an overall lobular architecture and are typically encased by a fibrous stroma. The lobules consist of multiple irregularly shaped tubular structures that have a double to several layered epithelial lin-
Appendageal tumours

Apocrine and eccrine differentiation have been suggested for cases with papillary tubular adenoma (2335). Terms tubulopapillary hidradenoma (705) and papillary tubular adenoma (2335) have been suggested for cases with apocrine and eccrine differentiation.

Histogenesis
Enzyme histochemistry (1361) and ultrastructural analysis (1361, 2394) have demonstrated tubular apocrine adenomas to be of apocrine differentiation.

Prognosis
Tubular apocrine adenomas are benign slow-growing neoplasms. Simple excision is curative.

Syringocystadenoma papilliferum

Definition
Syringocystadenoma papilliferum is a benign adnexal neoplasm that occurs in association with an organoid naevus such as naevus sebaceous in at least one-third of cases.

ICD-O code
8406/0

Synonym
Syringoadenoma

Epidemiology
Syringocystadenoma papilliferum occurs with equal frequency in both sexes. It is a tumour of childhood or adolescence, with many examples noted at birth. These lesions tend to increase in size at puberty, and sometimes multiply in number as well as becoming more papillomatous over time.

Clinical features
The majority of syringocystadenomas affect the head and neck area, typically as one or more warty papules, sometimes in a linear array, or as a solitary grey or red plaque. Scalp and neck are favoured sites; those on the scalp are typically alopecic. Syringocystadenomas may develop during puberty in a pre-existing naevus sebaceous, and at least one-third are associated with an underlying organoid naevus.

Histopathology
Histologically, endophytic invaginations of epithelium extend from the epithelial surface into the dermis. Typically squamous epithelium is present at the surface of the invaginations, and is contiguous with a double layer of cuboidal and columnar epithelium in the deeper portions of the lesion. Within the dermis, broad villous projections protrude into cystic spaces. Columnar epithelium is present toward the lumen of the spaces, and simple cuboidal epithelium can be seen at the periphery. Decapitation secretion of luminal cells is a frequent finding. Plasma cells are consistently numerous within the stroma, and are a highly reproducible finding in the stroma of syringocystadenomas.

The differential diagnosis includes hidradenoma papilliferum, which differs clinically by location in the perineal region, and histologically by dermal nodules showing a more complex papillary growth pattern, and absence of plasma cells in the stroma. The epithelial lining of the two lesions shows histologic overlap, however.

Precursor lesions
Approximately one-third of cases arise in organoid naevi.

Histogenesis
Syringocystadenomas show differentiation that is predominantly apocrine in pattern, but eccrine origin has been suggested in some cases, as exemplified by immunohistochemical labelling with eccrine marker IKH-4 (1109). An intriguing finding is the presence of IgA and secretory component within the epithelial cells in syringocystadenomas, and IgA and well as IgG within the plasma cells (2420). This observation suggests that plasma cells are attracted to tumour epithelium via a mechanism similar to that used by glands of the normal secretory immune system.

Somatic genetics
Allelic deletions of the patched gene 9q22 and loss of heterozygosity at 9p21.

Fig. 3.32 Syringocystadenoma papilliferum. A Keratinizing squamous epithelium at the surface merges with columnar epithelium in the deeper portions of the tumour. B Papillary projections are lined by pseud stratified columnar epithelium, and plasma cells are typically noted in the stroma.
Benign tumours with apocrine and eccrine differentiation

(p16) have been reported in syringocystadenoma papilliferum (281).

Prognosis and predictive factors
Syringocystadenomas are benign and simple excision is curative.

**Hidradenoma papilliferum**

Definition
Hidradenoma papilliferum is a benign cystic and papillary neoplasm that almost always develops in the vulval and perianal regions of middle-aged women.

ICD-O code 8405/0

Epidemiology
Most cases appear in women, although there are also reports in males (588, 1441,1697,2421). The neoplasm is rare in Black patients. The age of presentation ranges from 20-90 years (2428, 2435).

Localization
The skin of the vulva and perianal regions are the most frequently involved areas (588,1106,1441,1565,1568,1697, 2324,2421), although rare examples of extra-genital or ectopic hidradenoma papilliferum have been reported on postauricular skin (247), eyelids (1106, 1697,2056,2421), external auditory canal (1718), face (1106,1697) scalp (845), axilla (1106,2421), upper limb (2421), back (727,1106) and thigh (2421).

Clinical features
The lesion appears as a slow-growing cystic dermal nodule, usually asymptomatic, although it sometimes ulcerates and bleeds. The neoplasm is a unilateral skin-coloured nodule, papule or polypoid exophytic lesion, most commonly located on the labius majus.

**Histopathology**
At scanning magnification, hidradenoma papilliferum consists of a cystic neoplasm composed of elongated tubules and large papillary structures with a frond-like pattern. The papillae are composed of a central axis of connective tissue lined by two layers of epithelial cells. The basal layer is composed of pale-staining cuboidal myoepithelial cells and the luminal layer is made up by columnar cells with decapitation secretion. The cystic cavity and the lumina of the tubular structures contain apocrine secretions in the form of eosinophilic homogeneous material.

The epithelial cells at the periphery are flattened, and decapitation secretion is less evident, as a consequence of the pressure exerted by the cyst contents. The stroma surrounding the cystic cavity is composed of compressed fibrous tissue that is separated from the normal adjacent dermis by clefts. These clefts are responsible for the tendency of the neoplasm to shell out easily after incision of the epidermis.

In contrast with syringocystadenoma papilliferum, hidradenoma papilliferum is not connected with follicular infundibula and there are not plasma cells in the axis of connective tissue of the papillations. Sometimes, neutrophils are scattered within the connective tissue framework.

**Immunoprofile**
Immunohistochemical studies demonstrated that epithelial cells lining the papillations express low-molecular weight cytokeratins. The luminal border of the cells lining tubular structures is also decorated by carcinoembryonic antigen, epithelial membrane antigen and gross cystic disease fluid protein-15. Immunostains for S-100 protein and high-molecular-weight keratins are negative (2257). Neoplastic epithelial cells lining tubules and papillations also express strong immunoreactivity for androgen and oestrogen receptors (1739).

**Histogenesis**
Both the histopathologic and ultrastructural characteristics of hidradenoma papilliferum support an apocrine line of differentiation, although some authors have postulated the possibility of origin from Wolffian ducts or accessory mammary glands (576,1633).

Prognosis and predictive features
Hidradenoma papilliferum is a benign neoplasm cured by simple excision. Malignant transformation is a very uncommon event (588,1730,2274,2460). A case of adenosquamous carcinoma of the vulva developing from a pre-existing hidradenoma papilliferum has also been reported (142).

**Mixed tumour (chondroid syringoma)**

Definition
Cutaneous mixed tumours are benign adnexal tumours of skin composed of epithelial and stromal elements with a wide spectrum of patterns. These tumours are histologically analogous to mixed tumours of the salivary gland, but lack the tendency for local recurrence seen in the latter lesions.

ICD-O code 8940/0

Synonyms
Chondroid syringoma, mixed tumour of skin.

Epidemiology
Mixed tumours most often occur as solitary slowly growing nodules on the head

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Fig. 3.33 Hidradenoma papilliferum. A Hidradenoma papilliferum of the vulva. A polypoid exophytic lesion involving the left labius majus of an elderly woman. B The neoplasm shows a prominent papillary pattern. C Columnar cells shows evidence of decapitation secretion in their luminal border.
and neck of adults, although other sites may be affected. There is a male predilection. Most lesions are between 1-3 cm in diameter, although examples as large as 6 cm have been reported (1182).

Clinical features
Cutaneous mixed tumours present as asymptomatic dermal nodules, with no specific distinguishing clinical characteristics.

Histopathology
At low power, cutaneous mixed tumours are well-circumscribed lesions located in the dermis and/or subcutis. A biphasic growth pattern can be readily detected, with epithelial elements embedded within a myxoid, chondroid, or fibrous stroma. The epithelium often shows a pattern of branching tubules, sometimes with decapitation secretion suggesting apocrine differentiation. Solid cords and islands of epithelium as well as single cells may also be present. In some cases, the epithelial elements are composed of small non-branching tubules that may contain eosinophilic cuticles. Follicular differentiation occurs in some mixed tumours, in the form of follicular germinative cells, shadow cells, or sebocytes. Mixed tumours may exhibit clear cell change within the epithelial cells. In an estimated 40% of cases, mixed tumours contain hyaline cells characterized by an ovoid shape, dense groundglass or hyaline-like cytoplasm, and an eccentric nucleus (85). The cells resemble plasma cells, and have been called plasmacytoid cells. In some cases, hyaline cells are the predominant cell type, leading to the term hyaline-cell rich chondroid syringoma (735). The presence of hyaline cells appears to be of no prognostic significance, although such cells may present a diagnostic challenge to the unsuspecting pathologist (735).

Immunoprofile
Immunohistochemical studies reveal staining of the inner layer of epithelial cells with cytokeratin, CEA, and EMA, and staining of the outer cellular layer with S100 and vimentin (2559). The stroma of mixed tumours usually comprises at least half of the lesion, and may show variable patterns of differentiation, including myxoid, fibroblastic, fibrocartilagenous, chondroid, and even osteoid components. Combinations of matrix components are the rule. Despite the name chondroid syringoma, chondroid areas may be absent in the stroma. The stroma stains strongly for alcian blue with hyaluronidase resistance.

Differential diagnosis
In mixed tumours where stroma predominates, the differential diagnosis includes entities such as myxoma. In other lesions with abundant epithelial elements, the differential diagnosis includes benign adnexal tumours such as hidradenoma and syringoma, depending on the pattern of epithelial growth.

Histogenesis
It is generally accepted that there are both apocrine and eccrine variants of mixed tumours. Ultrastructural studies confirm that myoepithelial cells surround the epithelial cells, and appear to produce the stromal components of the lesions (2423). The stroma of mixed tumours contains matrix components such as types II and IV collagen, tenascin, fibronectin, and laminin (773). Ultrastructural and immunohistochemical studies of hyaline cells in mixed tumours suggest these cells derive from both the epithelial and stromal components of the lesions, possibly representing a regressive process (85).

Prognosis
Cutaneous mixed tumours are benign lesions cured by simple excision.
Malignant tumours with follicular differentiation

Pilomatrical carcinoma

Definition
Pilomatrical carcinoma is the malignant counterpart of pilomatrixoma.

ICD-O code 8110/3

Synonyms
Pilomatrix carcinoma, matrical carcinoma, invasive pilomatrixoma, malignant pilomatrixoma, matrix carcinoma.

Epidemiology
Pilomatrical carcinoma is an extremely rare tumour. Most cases present in adults with a broad age range (28,804,954, 2064). The mean age at the time of diagnosis is about 48 years. The male to female ratio is 2:1.

Etiology
The majority of pilomatrical carcinomas develop de novo, although malignant transformation from a pre-existing pilomatrixoma has been reported (2064). It is conceivable that proliferating pilomatrixoma, a variant of pilomatrixoma that occurs mainly in middle aged and elderly individuals, may represent an intermediate precursor lesion.

Localization
Pilomatrical carcinomas mostly occur in the head and neck, upper extremities and buttocks. Rare tumours have been reported in the axilla and inguinal regions.

Clinical features
The clinical appearance of pilomatrical carcinoma is generally not distinctive. Patients show solitary, occasionally ulcerated or fungating nodules ranging in size from 1-10 cm in diameter. Skin nodules are often of long duration ranging from several months to years before diagnosis, although occasional cases of recent onset and a history of rapid growth have been reported.

Histopathology
The tumour is a large, asymmetrical, poorly circumscribed dermal or dermal-subcutaneous mass composed of several, irregularly shaped and variously sized aggregations of basaloid cells (matrical and supramatrical cells) (28,804,954, 2064). Foci of cornified material containing shadow cells are characteristically observed within the basaloid cell aggregations. Some neoplasms show a variable desmoplastic stroma surrounding the basaloid cell aggregations. Focal connections of basaloid cell aggregations to the overlying epidermis and/or ulceration are often noted. Basaloid cells exhibit hyperchromatic nuclei, with one or more prominent nucleoli and ill-defined cytoplasmic margins as well as variable numbers of occasionally atypical mitotic figures (up to 10 mitoses per high-power field). Foci of geographical necrosis, calcification and ossification are observed. Mitotic activity is not a reliable indicator of malignancy, because mitoses are common in pilomatrixoma. Other parameters, such as an infiltrative growth pattern, as well as angiolymphatic, perineural, and bone invasion, are more reliable features (804,2064).

Immunoprofile
Immunohistological studies have previ-
ously revealed keratin staining in both basaloid and shadow cells (556).

**Prognosis and predictive factors**

Treatment of choice is by surgical excision with adequate margins. Mohs micrographic surgery technique may be useful in treating some patients. Pilomatrical carcinoma is a mainly locally aggressive tumour which often recurs if not completely removed but very rarely shows distant metastases. Metastatic spread is evidenced by involvement of regional lymph nodes, lungs and/or bone.

**Proliferating tricholemmal tumour**

**Definition**

Proliferating tricholemmal tumour is a solid-cystic neoplasm that shows tricholemmal differentiation similar to that of the isthmus of the hair follicle.

**ICD-O code**

8103/1

**Synonyms and historical annotation**

Epidermoid carcinoma in sebaceous cyst (252,416), subepidermal acanthoma (1458), proliferating epidermoid cyst (1152), invasive hair matrix tumour of the scalp (1910), trichochlamydocarcinoma (1053), giant hair matrix tumour (583), proliferating tricholemmal cyst (321), proliferating pilar cyst (68,92), proliferating follicular cystic neoplasm (23), proliferating tricholemmal cystic squamous cell carcinoma (1631), proliferating isthmic cystic carcinoma. These different names reflect the distinct histogenetic and biologic interpretations for this neoplasm among different authors.

**Epidemiology**

The neoplasm is more frequent in women than in men and most patients are elderly (2069).

**Localization**

More than 90% of the lesions are situated on the scalp. Other described locations, in decreasing order of frequency, include face, trunk, back and forehead (2069).

**Clinical features**

The tumour is a solitary, multilobular, large, exophytic mass, which may develop within a naevus sebaceous (866, 1874). Multiple lesions are very rare. The size ranges from 2-10 cm in diameter, although lesions up to 25 cm in diameter have been described (407). Alopecia and ulceration can be found.

**Macroscopy**

The lesions often show a multilobular appearance. The cystic structures often contain compact keratin and calcified material.

**Histopathology**

Proliferating tricholemmal tumour occurs on a morphologic continuum. On one end of the spectrum, it consists of a well-circumscribed solid and cystic neoplasm which involves the dermis and sometimes extends to the subcutaneous tis-
In addition to the typical features of a trichoepithelial (pilar) cyst, this tumour shows prominent epithelial infoldings into the cyst lumen. The epithelium shows peripheral palisading of small basoloid cells arranged along a thick vitreous membrane, differentiating towards large keratinocytes with ample eosinophilic cytoplasm and abrupt keratinization without a granular layer. Often, areas of calcification and abundant cholesterol crystals are seen within the compact eosinophilic keratin. The neoplastic cells are monomorphic without significant cytologic atypia and with only rare mitoses (1135,1724).

On the other end of the morphologic spectrum are neoplasms with malignant features such as invasive growth extending beyond the confines of the cyst wall coupled with nuclear pleomorphism and high mitotic activity. These areas may be indistinguishable from squamous cell carcinoma. Additional findings include shadow cells as an expression of focal matrical differentiation similar to that of pilomatricoma (1726), areas of sebaceous and apocrine differentiation (2021), and spindle cells (1649).

Differential diagnosis includes trichoepithelial cyst, which lacks the multilobular architecture, as well as proliferating epidermoid (infundibular) cyst (2069). The latter occurs most commonly in the anogenital region of male patients and shows a cystic cavity lined by stratified squamous epithelium with infundibular keratinization. Up to 20% of the lesions may undergo malignant transformation into squamous cell carcinoma (2069). Differentiation between proliferating trichoepithelial tumour and proliferating infundibular cyst is straightforward, because the former shows trichoepithelial keratinization, whereas the latter has mainly infundibular keratinization. Trichoepithelial carcinoma should also be considered.

**Immunoprofile**
Proliferating trichoepithelial tumour expresses fetal hair root cytokeratin, as well as cytokeratin 7 (933).

**Histogenesis**
The pathogenesis remains unknown. In some cases, human papillomavirus has been implicated in the etiology (23). It is unclear if proliferating trichoepithelial tumours arise de novo or from pre-existing trichoepithelial cysts (1631,1847).

**Prognosis and predictive factors**
Proliferating trichoepithelial tumours without atypical features generally behave in a benign fashion (762). Yet, complete excision is recommended to avoid recurrences, and to allow for complete histopathological evaluation. Tumours with an invasive growth pattern or cytologic atypia have an unpredictable course. They may be locally aggressive, recur, or metastasize (68,178,982,1017, 1537,1572,1727,1728,1773,2311,2486).

For this reason, it has been suggested that even the classical benign lesions are squamous cell carcinoma (1631).
Trichoblastoma

Definition
Trichoblastoma is a benign neoplasm differentiated toward the trichoblast, i.e., the folliculo-sebaceous-apocrine germ, or follicular germ, for short. In many cases, advanced follicular differentiation can be present also (28,989,1083).

ICD-O code 8100/0

Synonyms
Trichoepithelioma, trichoblastic fibroma, trichogenic trichoblastoma, trichohamartoma, sclerosing epithelial hamartoma, Brooke-Fordyce disease, Brooke-Spiegler disease.

Clinical features
Trichoblastomas, as a rule, are solitary, small papules that occur on any hair follicle-bearing location (usually head and neck), at any age, and can affect either sex. They can also present as multiple centrofacial papules or nodules, particularly in the diseases of Brooke-Fordyce and Brooke-Spiegler. The size of an individual neoplasm can vary from a few millimetres to several centimetres, but most are less than 1 cm in diameter. Most are skin-coloured and ulcerated only rarely.

The differential diagnosis is non-specific for solitary lesions, but includes the “angiofibroma” of tuberous sclerosis when multiple.

Histopathology
Trichoblastic epithelial components associated with stereotyped stroma, chiefly the follicular papilla, must be present to establish the diagnosis with surety. There are five patterns; these can be mixed in any given neoplasm. Large and small nodular trichoblastomas are usually circumscribed, sometimes subcutaneous, and contain a uniform distribution of solid trichoblasts with follicular papillae. In some cases, the follicular “papillae” are not papillary in that they fail to invaginate into the epithelial components of the germ. The epithelial cells are deeply basophilic, uniform, and overlap each other usually. Melanocytes can be prominent within the epithelial areas in some cases. Some cases have nodules that are lymphocyte-rich, a pattern termed originally lymphadenoma (1561,2053).

It should be noted that, rarely, lesions with a pattern similar to nodular trichoblastoma are really trichoblastic (basal cell) carcinomas that mimic trichoblastoma. While it is not completely understood what are all the factors that differentiate these lesion from trichoblastoma, one seems to be that the carcinomas infiltrate through skeletal muscle or other deep structures while there is a conspicuous absence of the usual stroma present in a classic nodular trichoblastoma. Rare examples with this pattern have metastasized (1960).

Retiform trichoblastomas are reticulated, with large fenestrations containing follicular stroma.

Cribriform trichoblastoma is the most common pattern when the neoplasms are multiple, characteristic of Brooke-Fordyce disease. The trichoblasts are usually fenestrated, but with small fenestrations compared to the retiform pattern. Racemiform trichoblastoma contains epithelial nests that simulate “clusters of grapes”. This results in stromal components that connect with the surrounding stroma rather than being isolated from it in fenestrations.

Columnar trichoblastoma (desmoplastic “trichoepithelioma”) occurs most commonly as a solitary depression on the face of a young woman. As a rule, these neoplasms are confined to the superficial dermis. They contain stereotyped, thin strands of epithelium compressed by dense stroma. Small trichoblasts can be seen in some cases, but are less common compared to conventional forms of
Benign tumours with follicular differentiation

trichoblastoma. The differential diagnosis includes morpheiform basal cell carcinoma, microcystic adnexal carcinoma, and, rarely, metastatic carcinoma from breast. Thus, superficial biopsies of such lesions should be investigated thoroughly, and additional biopsy or excision should be requested for cases in which the diagnosis is uncertain.

Immunoprofile
Trichoblastomas, as a rule, cannot be differentiated from basal cell (trichoblastic) carcinoma based solely on specific expression of cytokeratins. The presence of presumed Merkel cells within a neoplasm, however, does seem to favour trichoblastoma over basal cell carcinoma (1349). Some trichoblastomas can contain zones of ductal differentiation; when this occurs, markers, such as CEA will highlight those areas (2398) but they will not aid in establishing the diagnosis. Uncommonly, excessive pigmentation is seen in nodular trichoblastoma, and these lesions contain markers for melanocytes (1199), but they are nonspecific for the diagnosis, as basal cell (trichoblastic) carcinoma can have similar findings.

Desmoplastic trichoepithelioma contains AE14, EMA, and Leu-M1 (CD15) focally, but is negative for CEA and S100 (2511). CK 5, 8, 14 and 15 have been identified in some cases (2555). It can be differentiated from morpheiform basal cell carcinoma and microcystic adnexal carcinoma, in most cases, by applying CK20, which marks neuroendocrine cells in desmoplastic trichoepithelioma, but not in basal cell carcinoma or microcystic adnexal carcinoma (13). Furthermore, CK7 is usually positive in breast carcinoma metastatic to skin and in microcystic adnexal carcinoma, but not in desmoplastic trichoepithelioma. Stromelysin 3 has also been identified in the stroma of morpheiform basal cell carcinoma, but not in the stoma of desmoplastic trichoepithelioma (2346).

Prognosis and predictive factors
Because these are benign neoplasms, no treatment is required, in most cases, if the diagnosis is established with certainty. Because some trichoblastomas may occur, rarely, in association with basal cell (trichoblastic) carcinoma, and because of the difficulty in establishing the diagnosis in superficial biopsies, in some cases, additional biopsy or excision should be considered if there is uncertainty about the diagnosis.

Pilomatrixoma
Definition
Pilomatrixoma is a relatively common benign cutaneous adnexal neoplasm with differentiation towards the matrix and inner sheath of a normal hair follicle as well as hair cortex (28,1169).

ICD-O code 8110/0

Synonyms
Pilomatricoma, calcifying epithelioma of Malherbe, benign calcifying epithelioma

Epidemiology
Pilomatrixoma accounts for up to 0.2% of all routine dermatopathologic specimens
Appendageal tumours in certain centres. The tumour occurs in all age groups (1169). About 30-50% of cases present in young individuals less than 30 years of age. Previous studies have shown a female predominance.

Localization
Pilomatricomas favour hair-bearing areas, with the majority of cases arising in the head and neck region as well as upper extremities.

Clinical features
Patients present with solitary, asymptomatic, slowly growing, cystic or firm nodules measuring 0.5-3 cm in diameter (28,1169,1170). Lesions are commonly skin-coloured, but may show a bluish-purple to reddish hue or pigmentation. Unusual presentations include rapidly growing or giant tumours (measuring up to 15 cm in diameter), lesions with overlying striae or anetodermic changes, and multiple tumours. Multiple pilomatricomas are quite rare. They are a marker for myotonic dystrophy, and may rarely be associated with a number of different conditions including Rubinstein-Taybi syndrome, Turner syndrome, Goldenhar syndrome, sternal cleft defects, coagulative defects, and sarcoidosis. Pilomatricoma-like features are an occasional finding in cutaneous cysts removed from patients with Gardner syndrome.

Macroscopy
Grossly, pilomatricomas occur mostly as lobulated masses with variable amounts of chalky white or yellow keratinous material on their cut surfaces. Foci with bone may be observed.

Histopathology
There is usually a relatively well-circumscribed, deep dermal or dermal-subcutaneous, cystic neoplasm surrounded by a variable connective tissue stroma (28, 1169). A spectrum of histopathologic features reflecting mainly different stages of development is observed in individual lesions. Early and well-developed pilomatricomas are characterized by small to large-sized, cystic lesions lined focally by aggregations of basaloid cells (matri- cal and supramatrical cells) and few squamoid cells and filled centrally with large masses of eosinophilic cornified material (faulty hair matrix) containing shadow (ghost) cells as well as a few keratin filaments. A transition zone of retained nuclei from basaloid cells to eosinophilic cornified material containing shadow cells is focally observed. Basaloid cells exhibit deeply basophilic oval or round nuclei and a variable number of mitotic figures. Inflamed or regressing pilomatricomas are relatively large cystic tumours with prominent areas of shadow cells and foci of basa- loid and/or squamoid cells surrounded by a variable, often dense inflammatory infiltrate with histiocytic giant cells, and occasionally siderophages and/or melanophages. Areas of granulation tissue may be present. Occasional lesions dis-
play features of transepidermal elimination of shadow cells (perforating pilomatricoma) or a keratoacanthoma-like pattern. Old pilomatricoma lesions reveal no epithelial components but show irregularly shaped, partially confluent, focally calcified or metaplastically ossified shadow cell areas embedded in a desmoplastic stroma, with little or no inflammatory infiltrate. Extramedullary haematopoiesis has been observed in some regressing and old pilomatricoma lesions.

A subset of pilomatricomas, also termed “proliferating pilomatricoma”, is characterized by the presence of relatively large, solid or solid-cystic basaloid cell areas with small foci of shadow cells (1170). This variant presents mainly in middle aged and elderly individuals. “Matricoma” represents another unusual pilomatricoma variant characterized by discrete, small, solid aggregations of basaloid cells with several connections to pre-existing infundibula at different points (28).

**Molecular and cytogenetics**

Derivation of pilomatricomas from the hair matrix has been underlined by recent biochemical studies demonstrating prominent staining of tumour cells with antibodies directed against LEF-1, a marker for hair matrix cells. Mutations in the gene CTNNB1 have been detected in up to 75% of pilomatricomas studied implicating beta-catenin/LEF misregulation as a possible cause of hair matrix cell tumorigenesis (438). In another study, all 10 pilomatricomas examined were found to display strong bcl-2 immunostaining, a proto-oncogene well known to help in suppressing apoptosis in benign and malignant tumours (712). This finding supports a role for faulty suppression of apoptosis in the pathogenesis of pilomatricomas.

**Prognosis and predictive factors**

Treatment is recommended mainly to avoid a foreign body reaction and inflammation with eventual scarring. Surgical excision is usually curative, but occasional recurrences may be observed. Spontaneous regression has been reported in a few cases. Malignant transformation has only been suspected in a single case of pilomatrical carcinoma (2064).

**Tricholemmoma**

**Definition**

Tricholemmoma (TL) is a benign folliculoinfundibular proliferation occurring frequently but not exclusively on the face of adults. Multiple tricholemmomas may be associated with Cowden disease.

**ICD-O code**

Tricholemmoma 8102/0
Multiple tricholemmomas 8102/0

**Synonyms**

Trichilemmoma

**Epidemiology**

TL is a relatively common cutaneous proliferation that occurs mostly in adults and affects both sexes equally (323). Multiple TLs, often in conjunction with acral keratoses, palmar pits, and oral fibromas, are a cutaneous marker of Cowden disease (multiple hamartoma and neoplasia syndrome) (322,325,681,2025,2247,2249-2251).

**Localization**

TL arises on the head and neck, almost exclusively on the face, favouring the centrofacial area. Rarely, TL may occur in naevus sebaceous (410,1979).

**Clinical features**

Patients usually present with a solitary asymptomatic exophytic centrofacial lesion which is either wart-like with verrucous and keratotic features or dome shaped with a smooth surface. Individual lesions are small, varying in diameter between 3 and 8 mm (28). Multiple facial TLs are almost invariably associated with Cowden disease (2247,2249-2251).

**Histopathology**

Most cases of TL present as a sharply circumscribed superficial exo-endophytic proliferation with a papillated surface. There is marked parakeratosis, hyperkeratosis, and wedge-shaped hypergranulosis of the infundibula, in conjunction with a collarette of embracing adnexal epithelium (28,323). TL does not involve the interfollicular epidermis. The dominating histological pattern of TL is that of a bulbous infundibular hyperplasia with tricholemmal differentiation, akin to the outer root sheath of the hair follicle (28). There are one or more bulbous lobules, always in continuity with the epidermis. These lobules consist of numerous pale and clear isomorphic epithelia, most of which are PAS positive. At the periphery, pale columnar cells are arranged in a palisade, bordered by a prominent PAS-
and type IV collagen-positive basement membrane. Central foci of epidermal / infundibular keratinization, occasional small and inconspicuous squamous eddies, and keratinous microcysts in larger lesions are occasional findings (28). There are no mitoses.

Desmoplastic tricholemmoma is a variant of TL characterized by a highly desmoplastic stroma with broad zones of sclerosis and distinctive artifactual clefts. Instead of “pushing” smooth lobular contours there may be a pseudoinvasive interface akin to pseudocarcinomatous epithelial hyperplasia, simulating carcinomatous growth (1079,2333).

Differential diagnosis
Warts, basal cell carcinomas, squamous cell carcinomas, trichoblastomas, seborrheic keratoses, and keratosis follicularis inversa may contain areas of tricholemmal differentiation (31,1931). The tumour of the follicular infundibulum exhibits a plate-like pattern with interconnecting horizontally oriented epithelial strands. Inverted follicular keratosis consists of basaloïd and squamous epithelia, associated with large numbers of squamous eddies (i.e. concentric layers of squamous cells in a whorled pattern, sometimes keratinized).

Histogenesis
According to strict topographical anatomical criteria, TL arises from the follicular infundibulum and differentiates toward the outer [tricholemmal] root sheath (28). Its superficial folliculo-infundibular location militates against the classification of TL as a neoplasm of the lower portion of the hair follicle (i.e. the [outer] tricholemmal sheath). However, it is still a matter of debate whether TL is of hamartomatous/neoplastic (318,991,1906,1931) or of viral origin (15,28,31). The detection of HPV DNA in tricholemmomas by PCR (2688) favours the latter view of TL as a resolving verruca vulgaris with tricholemmal differentiation (15,28,31).

Prognosis and predictive factors
TL is an entirely benign cutaneous neoplasm. Multiple TLs are a hallmark of Cowden disease and should prompt a search for internal malignancy.

Trichofolliculoma

Definition
Trichofolliculoma (TF) is a follicularly differentiated hamartoma generally appearing during adult life.

ICD-O code 8101/0

Epidemiology
TF represents a rare hamartoma mostly occurring during adulthood (with a wide range of ages between 11 and 77 years (28)) without sex predilection (887).

Localization
TF favours the head and neck region, foremost the face. Most lesions are situated around the nose (887).

Clinical features
TF presents as a solitary asymptomatic dome-shaped lesion with a smooth surface and a widely dilated central ostium from which a small tuft of delicate white hairs emerges. Lesions are small, ranging between 0.5 and 1.0 cm in diameter (28).

Histopathology
The main histological features of TF are reflected by its “Caput Medusae” pattern (28): embedded in a highly fibrocytic stroma, large numbers of vellus follicles with upper and lower segments like those of normal follicles radiate from the perimeter of a dilated infundibulum.

TF is a symmetrical, well-circumscribed, vertically oriented lesion composed of three components: infundibulo-cystic, follicular, and stromal (28). The centre of the lesion is occupied by one or more widely dilated infundibulo-cystic structures that are continuous with the epidermis and open to the surface of the skin through an ostium. The cystic lumina may be filled with innumerable corneocytes and vellus hairs. From the epithelial walls of the infundibular cystic spaces smaller infundibula radiate, to which are attached vellus follicles in various numbers. These vellus follicles are not associated with muscles of hair erection or with sebaceous ducts, albeit sebaceous cells arranged as solitary units or in lobules may occur within the lining epithelium of the central infundibulo-cystic structure.

The morphology of the individual vellus follicles may vary from normal to strikingly aberrant (28). Normal vellus follicles may exhibit all stages of the follicular cycle (2106). The whole lesion is embedded in a cellular connective tissue sheath, which is separated from the adjacent normal dermis by prominent shrinkage clefts. The highly fibrocytic stroma.
which surrounds the individual vellus follicle resembles perifollicular sheath (28). The existence of considerable numbers of Merkel cells in all trichofolliculomas underlines their classification as hamartomas with follicular differentiation (967).

**Variants**

TF is a complex lesion with protean features (28). Some of these are caused by the evolutionary and devolutionary alteration of the vellus hair follicles in their regular biological cycles (2106). In this context, folliculo-sebaceous cystic hamartoma (1275,2187) may be interpreted as a TF at its very late stage with nearly complete regression of the transient follicular epithelium, but with concurrent growth and maturation of sebaceous elements (2105). Sebaceous trichofolliculoma (1846) exhibits distinct sebaceous lobules at its outer circumference, but lacks vellus follicles that radiate from the epithelial lining of the dilated infundibulum. The latter criterion militates against the classification of sebaceous trichofolliculoma as a true TF (28). Hair follicle naevus is regarded as a TF that was histologically sampled at its periphery (28). There is a striking predominance of mature vellus follicles and the central infundibular lumen may be quite inconspicuous.

**Prognosis and predictive factors**

TF represents an entirely benign cutaneous hamartoma with no reports of tumour progression or aggressive clinical course.

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**Pilar sheath acanthoma**

**Definition**

Pilar sheath acanthoma is a follicular neoplasm differentiated toward the permanent part of the hair follicle, to wit, the infundibulum and the isthmus. [The infundibulum is an extension of epidermis to meet the isthmus, but both function as part of the follicular sheath].

**Synonyms**

Infundibuloisthmicoma

**Clinical features**

Pilar sheath acanthomas affect adults of either sex, and are identified usually on the face. They are small, solitary papules up to 5 mm in diameter, with a central 1-2 mm punctum, lacking hair filaments, and will express corneocytes if squeezed. There are no known associated syndromes and no known genetic abnormalities within the neoplasms (29, 232,473,1570,2212,2402).

**Histopathology**

The classical example consists of a patulous infundibulum that connects with lobules of epithelium differentiated toward both the infundibulum and the isthmus. This differentiation results in blue-gray (infundibular) and pink (isthmic) corneocytes that fill the follicular canal. There can be a minor component of stem or bulb (or both) differentiation in some examples. Consequently there is, as a rule, no evidence of hair filaments in these neoplasms.

**Differential diagnosis**

Pilar sheath acanthoma should be differentiated from dilated pore (Winer), trichofolliculoma, and fibrofolliculoma/trichodiscoma. Dilated pore is an infundibular cyst that has proliferated minimally, but lacks isthmic differentiation. Trichofofolliculoma is a hamartoma and contains fully formed vellus hair follicles that radiate around a centrally positioned cyst. Fibrofolliculoma/trichodiscoma is also a hamartoma found characteristically in the Birt-Hogg-Dubé syndrome and that contains thin strands of infundibular epithelium connected so that fenestrations of delicate fibrous stroma are found within. Additionally, considerable stroma, lacking epithelium, is often identified (trichodiscoma).
Appendageal tumours

Prognosis and predictive factors
The neoplasm is benign; no treatment is necessary.

Tumour of the follicular infundibulum

Definition
Tumour of the follicular infundibulum (TFI) is a benign epithelial neoplasm of follicular origin.

Synonym
Infundibular tumour.

Epidemiology
TFI is an uncommon tumour occurring in adults, mainly after the age of 50. In two studies, TFI accounted for less than 10 per 100,000 skin samples. They can be observed on the face of patients with Cowden syndrome or on the surface of naevus sebaceous.

Localization and clinical features
Solitary TFI is mainly localized on the face and presents as a small flesh-coloured nodule, resembling basal cell carcinoma. Multiple or eruptive TFI present as hundreds of symmetrically distributed hypopigmented geographic macules localized on the face, neck, trunk, or on the periocular area. Sun exposure increases the contrast between normal skin and the tumours.

Histopathology
TFI is a plate-like horizontal proliferation of pale keratinocytes, which is localized in the papillary dermis and shows multiple connections with the overlying epidermis or with the infundibulum. The cells are paler and larger than normal keratinocytes and their cytoplasm stains with PAS. The tumour is sharply circumscribed and limited by a dense network of elastic fibres easily demonstrated by orcein staining. Desmoplastic and sebaceous variants have been described (557,1485).

Histogenesis
TFI derives from the normal follicular infundibulum. The occurrence of multiple TFI suggests a possible genetic basis, which remains to be established.

Prognosis and predictive factors
The prognosis is good, except in rare patients with multiple TFI who may develop basal cell carcinomas.

Fibrofolliculoma / trichodiscoma

Definition
Fibrofolliculoma and trichodiscoma are different developmental stages in the life of one single benign appendageal hamartomatous tumour, which differentiates towards the mantle of the hair follicle (27). Fibrofolliculoma represents the early and trichodiscoma the late stage in the development of this lesion (27).

ICD-O code
8391/0

Synonyms
Trichodiscoma first was erroneously thought to arise from or to differentiate toward the hair disk (Haarscheibe) and therefore bears this name (1836). Fibrofolliculoma was often used for perifollicular fibroma in the past. Neurofollicular hamartoma and trichodiscoma are the same (2048). "Mantleoma" was used as the overall term for both fibrofolliculoma and trichodiscoma (27).

Epidemiology
Fibrofolliculomas/trichodiscomas are rare appendageal tumours, occurring equally in males and females, usually not before the third decade of life.

Etiology
The etiology of the solitary lesions is unknown. The BHD gene was mapped to 17p11.2 (1256).

Localization
The preferred sites of location are the face, neck and chest.

Clinical features
Fibrofolliculomas and trichodiscomas cannot be distinguished clinically (248). The onset of the lesions is mostly in the third to fourth decade of life. They are skin coloured, smooth, dome-shaped papules, measuring 2-4 mm in diameter (248). The lesions are asymptomatic.

Histopathology
There is a histomorphological continuum between fibrofolliculoma and trichodiscoma. However, most of these presented cases were actually fibrofolliculomas which were merely prepared histologically in an unusual sectioning technique, resulting in misinterpretation as perifollicular fibroma (2107).
prominent stroma is made up of fine, fibrillar ribbon-like bundles of collagen, often arranged parallel to one another and perpendicular to the epithelial cords. The stroma contains numerous spindled fibrocytes and many venules and capillaries. Elastic fibres are markedly reduced. The stroma is often mucinous, comparable to the stroma of the follicular mantle-region.

**Trichodiscoma**

Trichodiscoma is a horizontally oriented dome-shaped tumour composed of more mesenchymal tissue than epithelial elements. A prominent tumour stroma of elliptical shape is seen, possessing the same cellular characteristics as in fibrofolliculoma. In peripheral zones of this prominent stroma, small groups of sebaceous lobules may be found. Mantle-like epithelial structures are uncommon. Plaque-like variants of fibrofolliculomas/trichodiscomas with confluence of single lesions and a resulting extension up to several cm in diameter have been described (2103).

The differential diagnosis of fibrofolliculoma includes trichofolliculoma at a late stage (2105). Fatty tissue is a typical finding in late stages of trichofolliculoma but not in fibrofolliculoma. Perifollicular fibroma/fibrous papule is also similar to fibrofolliculoma. However, it is usually devoid of mucin and shows no mantle-like epithelial proliferations (27). Trichodiscomas have to be differentiated from neurofibromas and cutaneous myxomas (521). However, the latter tumours lack the sebaceous epithelial component, typical of trichodiscoma.

**Immunoprofile**

The epithelial and mesenchymal parts of the lesions show the common reactivities to cytokeratins and vimentin. The tumour stroma is strongly reactive with antibodies to CD34, reflecting its differentiation towards the follicular mantle region.

**Histogenesis**

Histologic and immunohistologic data suggest that fibrofolliculoma/trichodiscoma is derived from/differentiated to the mantle region of the hair follicle (27,521). The mantle region is a specialized epithelial-mesenchymal structure, located at the lower end of the follicular infundibulum (606) and is the source and starting point for the development of the sebaceous glands (27). Fibrofolliculoma/trichodiscoma is considered to be a hamartomatous lesion. Its mesenchymal part may be responsible for the origin and growth of the whole lesion, leading to the distinctive mesenchymal-epithelial proliferation, reminiscent of a deformed mantle region (2103). The postulated cell of origin therefore might be a specialized dermal dendritic spindle cell, normally situated in the mantle region (521,2103).

**Genetic susceptibility**

Multiple fibrofolliculomas/trichodiscomas are part of the Birt-Hogg-Dubé syndrome (BHD), an autosomal inherited syndrome, also affecting the lung and kidney (248,2579). The BHD gene is located at 17p11.2 (806) and encodes folliculin whose function is unknown. The patients may have multiple, often bilateral renal carcinomas, frequently representing unusual histological subtypes. They also have an increased frequency of spontaneous pneumothoraces.

**Prognosis and predictive factors**

Fibrofolliculoma/trichodiscoma is a benign lesion, excised primarily for cosmetic reasons. However, it is an important marker for Birt-Hogg-Dubé syndrome and its associated complications.
Sebaceous carcinoma

Definition
Sebaceous carcinoma (SC) is a cytologically- and/or architecturally- malignant neoplasm demonstrating exclusive sebocytic differentiation.

ICD-O code 8410/3

Historical annotation
Historically, SCs have been subcategorized into ocular and extraocular subtypes (1510A, 1696A, 1827A, 1856A, 2511A, 2609A), although there is no inherent biological difference between such lesions.

Epidemiology
SC usually arises in adults, with an average patient age of 62 yrs. and a female predominance, by a factor of roughly 2:1. Tumours of the eyelids are preferentially seen in Asian patients, and also may represent a complication of prior radiotherapy (1067A).

Clinical features
All SCs present as painless masses, which can be multifocal. In the ocular adnexae, they may be mistaken clinically for chalazions, blepharitis, cicatricial pemphigoid, or conjunctivitis (642, 839, 2542). In extraocular sites, sebaceous malignancies are commonly confused with basal cell carcinomas and squamous cell carcinomas. Most extraocular SCs are encountered in the skin of the head and neck, followed by the trunk, genitals, and extremities. Rare cases may also be seen in the mouth, salivary glands, lungs, and breasts.

Macroscopy
SCs are nodules that typically enlarge slowly but may occasionally grow rapidly; some become ulcerated. A minority of individuals with this tumour have the Muir-Torre syndrome (2227).

Histopathology
Sebocytic differentiation, typified by multivesicular and vacuolated clear cytoplasm, is the sine qua non for sebaceous neoplasms including SC. It must be separated from simple cytoplasmic clarity, a microscopic change that is relatively common in cutaneous neoplasms of many other lineages (2294). SCs are organoid proliferations comprising dermal lobules of variably-atypical polygonal cells, with a fibrovascular stroma that typically lacks desmoplasia. Central portions of the tumour cell nests may be necrotic, yielding a “comedo” growth pattern. The cells of well-differentiated neoplasms show abundant cytoplasm and oval vesicular nuclei with distinct nucleoli; mitotic figures are variable in number. On the other hand, more poorly-differentiated SCs show high nuclear-to-cytoplasmic ratios, nuclear pleomor-
phism, prominent nucleoli, brisk mitotic activity - sometimes with pathologically-shaped forms - and amphophilic or basophilic cytoplasm. Intracellular vacuoles are sometimes not seen easily in those lesions, and may require the use of special histochemical stains, such as the oil-red-O or Sudan IV methods, to detect them (2540).

The grading of SCs - into grades I through III - is based on growth patterns rather than on their cytological features (1892). Tumours that are constituted by well-demarcated, roughly equally-sized cellular lobules are graded as I; those with an admixture of well-defined nests with infiltrative profiles or confluent cell groups are grade II lesions; and grade III SCs exhibit highly-invasive growth or a medullary sheet-like pattern.

All SCs have the potential for an association with overlying carcinoma in-situ (CIS), or extramammary Paget disease (EPD) of the sebaceous type, or both, in the surface epithelium and in other epidermal appendages (especially pilosebaceous units) (448,1702). The latter lesions are probably marker lesions that represent a cutaneous “field” defect, rather than being direct precursors of, or extensions from, underlying SC. This premise has support from occasional cases in which only intraepithelial sebaceous carcinoma is present, in the absence of an invasive component in the dermis (1510). In pragmatic terms, however, one should always consider the possibility of infiltrative SC whenever EPD or carcinoma in-situ is seen in a superficial biopsy.

Variants
Selected microscopic variants of SC deserve special comment because they may engender interpretative confusion with other cutaneous tumours (2540, 2542).

Basaloid SC comprises small cells with scant cytoplasm, and may often show nuclear palisading at the periphery of cellular nests. It commonly manifests a grade III growth pattern, and overtly-sebocytic elements are sparse and difficult to identify as such.

Squamoid SC shows prominent squamous metaplasia, often with keratin pearl formation; some examples may also demonstrate spindle-cell areas, equating with a sarcomatoid image.

Still other examples of SC may demonstrate pseudo-neuroendocrine organoid growth, focally resembling the pattern of “carcinoid” tumours (1235). Based on these brief descriptions, one could easily predict that basal cell carcinoma, squamous cell carcinoma, neuroendocrine tumours, epithelial malignancies with potential spindle-cell differentiation, and a variety of clear-cell neoplasms in the skin may enter differential diagnostic consideration in selected cases of SC.

Immunoprofile
SC shows immunoreactivity for several generic epithelial markers such as pankeratin, epithelial membrane antigen (EMA), CD15, CU18, CA15.3, and Thomsen-Friedenreich antigen (75). EMA labeling may enhance the cytoplasmic “bubbliness” of the tumour cells in this neoplasm. That pattern is distinctive, but it is not observed in all examples of SC. Reactivity for androgen receptor protein and human milk fat globule protein-2 also has been reported in SC (182,2191). However, it is not yet know whether the latter markers are diagnostically helpful in excluding other clear-cell tumours.

Genetic susceptibility
Immunoreactivity in SC for various DNA-mismatch repair gene products, especially for MSH-2, has been correlated with a relationship to the Muir-Torre complex (1468,1536). However, virtually no systematic data are available on the detailed genetic profiles of either sporadic or syndromic SC.

Prognosis and predictive factors
Both ocular and extracutaneous SCs have a 30-40% risk for local tumour recurrence, 20-25% for distant metastases, and 10-20% for tumour-related mortality (1645). Some reports appear to support the premise that immunoreactivity for mutant p53 protein at a level of >10%, and for proliferating cell nuclear antigen at a level of >25% may be linked to an adverse outcome (977). A similar comment may apply to those lesions that overexpress the c-erbB-2/HER-2/neu protein (472,977).

Sebaceous adenoma
Definition
Sebaceous adenoma is a small tumour composed of basaloid cells and fully differentiated sebocytes.

Fig. 3.48 Sebaceous adenoma. A Well circumscribed lobulated sebaceous tumour. Fully differentiated sebocytes predominate and epidermis is replaced by the tumour. B High magnification of the periphery of the lobule.
Appendageal tumours

ICD-O code 8410/0

Epidemiology
Sebaceous adenomas occur mostly as solitary lesions in persons older than forty years (1993). Lesions are located usually on sun-damaged skin of the head and neck area. Rarely patients have multiple lesions (2258), then the possibility of Muir-Torre syndrome should be considered.

Clinical features
Sebaceous adenomas are relatively small yellowish tumours often covered by a scale or crust (2353).

Histopathology
This well-circumscribed tumour is made up of small lobular aggregations of sebocytes with a rim of basaloid cells at the periphery, recapitulating the maturation of sebocytes from the periphery to the centre comparable to normal sebaceous glands (1542). Lobules are composed of vacuolated fully differentiated sebocytes and these cells predominate markedly over the basaloid sebocytes. Sebaceous adenoma is often connected to the overlying epidermis, and may be covered by a thick plug of keratin and disintegrated sebocytes. Ductal structures are rare, as are mitotic figures. Sebaceous adenoma has to be differentiated from sebaceous hyperplasia, where the sebaceous lobules are arranged around a central placed follicular infundibulum that is connected to the epidermis. In sebaceous hyperplasia the epidermis may show changes mimicking seborrhoeic keratosis. Sebaceomas are nodular lesions of basaloid undifferentiated sebocytes and only a few small groups of vacuolated sebocytes. There may be morphological overlaps between sebaceous adenoma and sebaceoma. The term sebomatrixoma was introduced as an attempt to simplify the nomenclature of the different benign sebaceous adnexal tumours and to summarize them under one name (2003).

Genetics
Little is known about the genetics of sebaceous adenoma. Most of the tumours occur as solitary lesions but a few examples of SA are part of the spectrum of different sebaceous tumours in MTS. By immunohistochemistry it is possible to look for a loss of MSH-2, MLH-1 repair proteins. Tumours related to a mismatch repair gene defect show a microsatellite instability in a high percentage (1334).

Prognosis and predictive factors
Sebaceous adenomas are benign tumours. If the patient has Muir-Torre syndrome, the prognosis depends on the associated internal malignancies.

Sebaceoma

Definition
Sebaceoma is a benign, adnexal neoplasm with sebaceous differentiation. It is characterized by multiple, smooth-bordered lobules and cystic spaces composed primarily of immature sebaceous cells admixed with randomly scattered mature sebocytes.

ICD-O code 8410/0

Synonyms
Sebaceous epithelioma, basal cell epithelioma with sebaceous differentiation, and sebomatricoma.

Epidemiology
Sebaceomas are rare sebaceous neoplasms that may be associated with the Muir-Torre syndrome (1624,2114). They typically arise in late adulthood with the mean age of diagnosis being at approximately 70 years of age, but may be seen in early adulthood (2378). The tumours have a predilection for females.

Localization
Sebaceomas occur mainly on the face and scalp, with rare cases reported on the trunk (226,636,1710,1749,1922,2258,2378).

Clinical features
Clinically, sebaceomas present as yellow to orange solitary papules on the head and neck (636,2258,2378). Those lesions associated with the Muir-Torre syndrome may be multiple (347,1624,2114). They are slow-growing neoplasms and do not recur after excision (636,2258,2378).

Histopathology
Architecturally sebaceoma is composed of multiple well-circumscribed lobules of various size centred on the dermis. The lobules often contain ducts and cystic...
areas containing holocrine secretion and only rarely do they connect with the overlying epidermis. A brightly eosinophilic cuticular material lines both the ducts and cysts, similar to what is seen in the normal sebaceous ducts. Cytologically the neoplasm is comprised predominantly of small, uniform basaloid cells with bland nuclear features admixed with haphazardly distributed mature-appearing sebaceous cells. The mature sebaceous cells have abundant vacuolated cytoplasm and ovoid nuclei, which often have a scalloped nuclear membrane. Rare typical mitoses may be seen, however, atypical mitosis and necrosis are not features of sebaceoma. The surrounding stroma is dense, eosinophilic connective tissue. There is no cleft seen between the neoplasm and the stroma, as is the case with basal cell carcinoma. A wide variety of patterns have been described for sebaceoma, sometimes even within the same neoplasm. These include reticulated, cribriform and glandular (634,1710). There have been reports of a variant with eccrine differentiation, a pigmented variant and a sebaceoma that arose in a seborrhoeic keratosis (226,1749,1922). Those lesions that arise in Muir-Torre syndrome may have a keratoacanthoma-like architecture (347).

**Immunoprofile**
Immunohistochemistry demonstrates positivity with high-molecular weight keratin. EMA stains most mature sebocytes, and thus will only show positivity of the mature vacuolated sebaceous cells scattered amongst the tumour, while the basoloid cell compartment will be negative (1710). Several reports have demonstrated loss of heterozygosity as well as microsatellite instability in a marker gene located near hMSH2 in patients with sebaceoma and Muir-Torre syndrome (1332,1536). By immunohistochemistry it is possible to look for a loss of MSH-2, MLH-1 repair proteins (1334).

**Prognosis and predictive factors**
Sebaceoma is a benign neoplasm that does not recur after treatment or metastasize. It may be a marker of Muir-Torre syndrome, in which case the patient has a high risk of internal malignancies.

**Cystic sebaceous tumour**

**Definition**
Cystic sebaceous tumour is a large distinctive tumour with is almost always associated with Muir-Torre syndrome (MTS) (1999).

**ICD-O code**
8410/0

**Epidemiology**
Cystic sebaceous tumours occur nearly exclusively in MTS, which is a phenotypic variant of the hereditary non polyposis colon cancer syndrome (HNPCC). MTS is inherited in an autosomal-dominant fashion and is caused by genetic alterations within the DNA mismatch repair system. Patients often have a family history of malignancies and most are affected with a variety of internal malignancies such as colon cancer, urothelial cancer, endometrial cancer and others. MTS patients develop a broad spectrum of different sebaceous skin tumours, which may be difficult to classify (347, 1624), and keratoacanthomas. Among the sebaceous tumours, CSTs are unique because they serve as diagnostic markers for the syndrome. MTS has a male preponderance and is clinically diagnosed mostly in adults older than 40 years.

**Localization**
The upper trunk is the most common location.

**Clinical features**
CSTs are usually solitary, but rarely can be multiple. They resemble hair follicle cysts and present as dermal nodules. In patients diagnosed with internal malignancies CST is often excised in order to rule out a metastatic skin lesion.

**Histopathology**
CST are large, well circumscribed dermal tumours which may connect to the upper dermis, and usually extend into the subcutis. The outer surface of the neoplasm may be obscured in cases with an accompanying granulomatous inflammation due to the ruptured cyst wall. Well-differentiated CST show a cystic growth pattern with a small line of basaloid undifferentiated sebaceous matrix cells at the periphery and a broad zone of fully differentiated vacuolated sebocytes towards the centre of the cystic tumour. Well-differentiated CST do not show cytological atypia, and have only few mitoses. Ductal structures may be seen in the cyst wall. Proliferation of tumour cells produces infoldings of the cyst wall in some CST. The more solid variants are predominantly composed of undifferentiated sebaceous cells with mitotic figures and variable cytologic atypia.

**Genetics**
Germline mutations of the DNA mismatch repair genes are responsible for MTS. In the vast majority of cases the associated tumours show a complete loss of the corresponding mismatch repair protein (MSH2 or MLH1). This can be demonstrated immunohistochemically by antibodies directed against MSH2 and MLH1 protein (1469,1536,2227). A loss of the nuclear staining for one of these antibodies within the tumour cells accompanied by a positive staining of nuclei in the surrounding tissue strongly suggests loss of the corresponding DNA mismatch repair protein. Typically, these tumours show high microsatellite instability (1332, 1469, 1999).

**Prognosis and predictive factors**
Some authors interpret cystic sebaceous adenoma as a variant of sebaceous carcinoma (1733). So far there is no clinical evidence that these tumours in any case represent malignant sebaceous tumours (872,1624,1999). Because of these conflicting views, complete excision is recommended. The prognosis in MTS is determined by the nature of the associated internal malignancies. In most cases CST develops after the first internal malignancy, but in up to 25% of cases they represent the first clinical sign of MTS. Even in a patient with a solitary CST who does not fulfill the clinical criteria for MTS, a molecular genetic analysis may show a germline mutation in a mismatch repair gene (1333). Because of the specific marker function of CST it is possible to detect patients and families with an inherited DNA mismatch repair defect predisposing to various types of internal cancer.
Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotype, genotype, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Some lymphomas present only in the skin, but never primarily in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities.

The members of the WHO Working Group, together with their colleagues from EORTC, were able to formulate a classification that respects the many unique features of skin lymphomas but avoids a terminology restricted to primary cutaneous lymphomas. We are confident that this proposal will be used by pathologists and dermatologists world-wide for years to come.
### WHO / EORTC classification of cutaneous lymphomas

<table>
<thead>
<tr>
<th>Malignant T-cell and NK-cell neoplasms</th>
<th>Mycosis fungoides</th>
<th>9700/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagetoid reticulosis (localized disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular, syringotropic, granulomatous variants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatous slack skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sezary syndrome</td>
<td>9701/3</td>
<td></td>
</tr>
<tr>
<td>CD30+ T-cell lymphoproliferative disorders of the skin</td>
<td>9718/1</td>
<td></td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
<td>9718/3</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma**</td>
<td>9708/3</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous peripheral T-cell lymphoma (PTL), unspecified</td>
<td>9709/3</td>
<td></td>
</tr>
<tr>
<td>Subtypes of PTL (provisional)</td>
<td></td>
<td></td>
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<tr>
<td>Primary cutaneous aggressive epidermotropic</td>
<td></td>
<td></td>
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<tr>
<td>CD8-positive cytotoxic T-cell lymphoma</td>
<td></td>
<td></td>
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<tr>
<td>Cutaneous gamma/delta-positive T-cell lymphoma</td>
<td></td>
<td></td>
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<tr>
<td>Primary cutaneous small/medium CD4+ T-cell lymphoma</td>
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<td></td>
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<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td>9719/3</td>
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<tr>
<td>Hydroa vacciniforma-like lymphoma (variant)</td>
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<td></td>
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<tr>
<td>Adult T-cell leukaemia/lymphoma*</td>
<td>9827/3</td>
<td></td>
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<tr>
<td>Angioimmunoblastic T-cell lymphoma*</td>
<td>9705/3</td>
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</table>

<table>
<thead>
<tr>
<th>Malignant B-Cell neoplasms</th>
<th>Cutaneous marginal zone B-cell lymphoma (MALT-type)</th>
<th>9699/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous follicle centre lymphoma</td>
<td></td>
<td>9690/3</td>
</tr>
<tr>
<td>Cutaneous diffuse large B-cell lymphoma</td>
<td></td>
<td>9680/3</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma*</td>
<td></td>
<td>9680/3</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis*</td>
<td></td>
<td>9766/1</td>
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<tr>
<td>Chronic lymphocytic leukaemia*</td>
<td></td>
<td>9823/3</td>
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<tr>
<td>Mantle cell lymphoma*</td>
<td></td>
<td>9673/3</td>
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<tr>
<td>Burkitt lymphoma*</td>
<td></td>
<td>9687/3</td>
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</table>

<table>
<thead>
<tr>
<th>Immature haematopoietic malignancies</th>
<th>Blastic NK-cell lymphoma *** /</th>
<th>9727/3</th>
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</thead>
<tbody>
<tr>
<td>CD4+/CD56+ haematodermic neoplasm</td>
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<td></td>
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<tr>
<td>Precursor lymphoblastic leukaemia/lymphoma</td>
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<td></td>
</tr>
<tr>
<td>T-lymphoblastic leukaemia*</td>
<td></td>
<td>9837/3</td>
</tr>
<tr>
<td>T-lymphoblastic lymphoma*</td>
<td></td>
<td>9729/3</td>
</tr>
<tr>
<td>B-lymphoblastic leukaemia*</td>
<td></td>
<td>9836/3</td>
</tr>
<tr>
<td>B-lymphoblastic lymphoma*</td>
<td></td>
<td>9728/3</td>
</tr>
<tr>
<td>Myeloid and monocytic leukaemias*</td>
<td></td>
<td></td>
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</tbody>
</table>

| Hodgkin lymphoma* |                  |       |

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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (786) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

* Extracutaneous lymphomas frequently involving the skin as a secondary site are printed in italics.

** Definition is restricted to lymphomas of alpha/beta T-cell origin.

*** Recent evidence suggests an origin from a dendritic cell precursor. In recognition of uncertain histogenesis, the term CD4+/CD56+ haematodermic neoplasm is preferred.
## TNM classification of cutaneous T-cell lymphomas (CTCL)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>T1 Limited lesions covering &lt;10% of the skin surface</td>
<td>N0 no palpable lymph nodes, pathology negative for CTCL</td>
<td>M0 no involvement of visceral organs</td>
</tr>
<tr>
<td>Ib</td>
<td>T2 generalized lesions covering 10% and more of the skin surface</td>
<td>N0 no palpable lymph nodes, pathology negative for CTCL</td>
<td>N0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IIa</td>
<td>T1 Limited lesions covering &lt;10% of the skin surface, or T2 generalized lesions covering 10% and more of the skin surface</td>
<td>N1 palpable peripheral lymph nodes pathology negative for CTCL</td>
<td>M0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IIb</td>
<td>T3 tumours, one or more</td>
<td>N0: no palpable lymph nodes, pathology negative for CTCL or, N1 palpable peripheral lymph nodes, pathology negative for CTCL</td>
<td>M0 no involvement of visceral organs</td>
</tr>
<tr>
<td>III</td>
<td>T4 generalized erythroderma</td>
<td>N0: no palpable lymph nodes, pathology negative for CTCL or N1 palpable peripheral lymph nodes, pathology negative for CTCL</td>
<td>M0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IVa</td>
<td>T1-4</td>
<td>N2: no palpable peripheral lymph nodes, pathology positive for CTCL or N3: palpable peripheral lymph nodes, pathology positive for CTCL</td>
<td>M0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IVb</td>
<td>T1-4</td>
<td>N0-3</td>
<td>M1 involvement of visceral organs</td>
</tr>
</tbody>
</table>

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Modified, from Refs. (333, 344, 2537).
WHO / EORTC Classification of cutaneous lymphomas

The skin is the second most common site of extranodal lymphoma, following the gastrointestinal tract (340). Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Because the clinical implications of primary and secondary cutaneous lymphoma are different, the dermatologist and pathologist should be familiar with both types of neoplasms. For this reason it also is problematic to use a classification system restricted to primary cutaneous lymphomas (2523). It is important for dermatologists, haematoncologists, and pathologists to use a unified system for the diagnosis and treatment of cutaneous lymphoma (1858).

Nevertheless, cutaneous lymphomas present some unique clinical aspects. There are some diseases that present only in the skin, and are never primary in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotype, genotype, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities. These differences may be related to stage or tumour burden, or more fundamental biological differences. For example, some lymphomas composed of large centrocytes and centroblasts have an indolent clinical course when presenting as a localized cutaneous tumour, but a similar cytological process in lymph node would be considered aggressive, i.e. diffuse large B-cell lymphoma.

Dermatologists, haematoncologists, and pathologists must use a common language. In this spirit we utilize the WHO classification of lymphoid neo-

plasms (1121), but we expand upon the unique features of many cutaneous lymphomas to emphasize their distinctive clinical and biological characteristics (336A,2522). Additional clinical and morphological variants have been added, where appropriate, in order to comprehensively cover the many manifestations of cutaneous lymphoma. Atypical reactive lesions that may represent precursors of cutaneous lymphoma are discussed where relevant (336A,2522).

Cutaneous lymphoproliferative disorders (CLD)

These include reactive lymphoid hyperplasias (so called cutaneous “pseudolymphomas”), prelymphomatous conditions and definite malignant lymphoma of low grade or of high grade malignancy. According to their biologic behaviour, CLD can be subgrouped into prognostic categories which are not reflected in the classifications, which however are of special interest for the patient and for the treating physician.

When diagnosing a cutaneous lymphoproliferative disorder, both the clinico-pathologic classification and the biologic category should be considered. The advantage of such an approach is to provide the diagnosis according to the current WHO-classification of lymphomas, and in addition, to include essential information about the biologic behaviour, which may be significantly different than that of the nodal counterpart. These data are crucial for the clinician involved in counseling and treatment of the patient.

Reactive lymphoid hyperplasias (RLH) (pseudolymphomas)

These are reactive benign lymphoproliferative processes, localized or disseminated, which heal either spontaneously after elimination of the causative factor (e.g. drugs) or after treatment with non-aggressive (no severe side effects to be expected after long term application) modalities, and which do not recur after removal of the causative agent.

Prelymphomatous (“abortive”) disorders (PLD)

PLD show a chronic long-standing course, no spontaneous regression in most cases, and no extracutaneous spread with involvement of visceral organs. In some cases, clonality of the infiltrate can be demonstrated. However, in most cases the neoplastic cell clone never overcomes host control mechanisms and cannot expand and therefore does not convert into definite malignant lymphoma. Survival time is not affected. Definite malignant lymphoma of low-grade malignancy (LLM). This category includes cutaneous lymphomas that show a slowly progressive course with systemic spread in later stages and have the potential for transformation into more aggressive high-grade malignant lymphomas. Survival time usually is greater than 5 years.

Definite malignant lymphoma of high-grade malignancy (LHM)

These diseases are characterized by a more rapid course than the low-grade lymphomas and usually exhibit a bad prognosis with survival times less than 5 years.
Mycosis fungoides

Definition
Mycosis fungoides (MF) is the prototype of cutaneous T-cell lymphomas (CTCL) and can be defined as a peripheral, epidermotropic non-Hodgkin T-cell lymphoma of low grade malignancy initially presenting in the skin and showing step-wise clinical progression from patches to plaques and tumours, and distinct histological (except in early stages), phenotypic and genotypic features.

ICD-O code 9700/3

Synonyms and historical annotation
In 1806 Jean-Louis Alibert (1768-1837) presented an extraordinary skin disease which he described in detail under the name of “Pian fungoides” in 1814 and as “Mycosis fungoides” in 1832 (58). At his time the etiology of the disease was completely unclear. It is worth noting that Alibert in 1832 copied part of the text from Bontius (283). Ernest Bazin (1807-1878) published three different stages: Période érythematous stage: red colored patches) Période lichenoid (the lichenoid stage: itching and different plaques with small papules). Période fongoïdique, mycositique (fungal stage: mushroom-like tumours of different size).

Epidemiology
The incidence of MF from 1973 through 1992 in the USA was 0.36/ 100,000 persons per year (2445). Most frequently MF affects adults, usually in their 5th-6th decade, with a male to female ratio of approximately 2:1 and a preponderance of black (1.7) vs white populations. The increase of frequency paralleled by a decrease of mortality rates between 1979 and 1991 (2485) most probably is due to changing criteria resulting in over-diagnosing MF by including non-neoplastic conditions into this group. Data collected by the Surveillance, Epidemiology and End Results Program (SEER) of the US National Cancer Institute indicate that the relative survival changed little after 11 years, at which point it was 66% (2485).

Etiology
The etiology of MF is unknown. The role of environmental antigens, viruses or bacteria is controversial (2605).

Localization
All parts of the skin may be involved without any predilection site.

Clinical features
Clinically MF is characterised by a step-wise evolution with sequential appearance of patches, plaques and tumours. Patches are circumscribed lesions with discolouration and sometimes little scaling, without palpable infiltration of the skin. Plaques usually evolve out of patches and present with palpable infiltration of various degree (thin and thick plaques). Tumours exhibit an exophytic growth in most of the cases and tend to ulcerate. In advanced stages of the disease there may be spread into the peripheral blood, involvement of lymph nodes, bone marrow and internal organs. Besides physical examination, including mapping of skin lesions and photodocumentation, a skin biopsy for paraffin embedding and for cryo-preservation should be taken, preferentially at multiple sites. Additional investigations include blood cell counts with PAS staining for Sézary cells, chest x-ray and CT-scan of abdomen and of peripheral lymph nodes. There is no need for taking a bone marrow biopsy in early patch and plaque stages of MF without atypical cells in the peripheral blood. Biopsy of enlarged lymph nodes is mandatory.

Tumour spread and staging
MF, like other cutaneous lymphomas, is a systemic disease with preferential homing and proliferation of neoplastic lymphocytes into the skin. Therefore skin lesions may spread all over the body sur-

Fig. 4.1 Mycosis fungoides. A Large patches involving hip and abdomen. B Plaque-stage MF affecting the left arm. C Medium-sized hyperconvoluted cerebriform cells with prominent cytoplasmic halos in the epidermis, aligned within the basal layer.
face. Spread to extracutaneous compartments occurs in advanced stages of the disease, due to change or loss of homing receptors. These changes are usually accompanied by a change of cytomorphology of the tumour cells from small cerebriform to medium-sized pleomorphic or large blast-like cells.

**Histopathology**

The histologic diagnosis of MF is based on numerous subtle changes, most of which may be present to some degree in many inflammatory and neoplastic cutaneous conditions. The most significant criteria, which however in early lesions often are missing or are only present in part, are Pautrier microabscesses, exocytosis of lymphocytes, disproportionate epidermotropism. The presence of cells with hyperconvoluted cerebriform nuclei in the epidermis larger than dermal lymphocytes, or lymphocytes in clusters in the dermis, and lymphocytes aligned within the basal layer without or with only little spongiosis and without prominent vacuolisation in the dermo-epidermal junction are typical but not specific features. Haloed lymphocytes have proved to be the most robust discriminator of MF from non-MF.

**Patch stage**

The diagnosis is usually based on a combination of specific histologic criteria, without the necessity of confirmatory immunophenotyping (2058,2059,2213). Whereas in very early "prelymphomatous" patch stages the histological picture often is non-specific, the histological findings become diagnostic in the thin plaque stage, when a denser infiltrate with lymphocytes lining up in the basal layer, especially at the tips of the rete ridges with epidermotropism of single cells is present. The majority of cells are small, differentiated lymphocytes with round or only slightly cerebriform nuclei. Haloed cells may predominate in the epidermis in early patch lesions of patients with otherwise advanced disease. In addition, there can be mild acanthosis, hyperkeratosis, signs of basal layer damage (pigment incontinence), edema or fibrosis of the papillary dermis. There is proliferation of postcapillary venules with prominent endothelial cells, simulating giant cells. The infiltrate may contain an admixture of eosinophils, plasma cells, macrophages, and dermal dendritic cells (922,2156).

**Thick plaque stage**

This is typified by a dense, subepidermal, usually band-like infiltrate containing a high number of cerebriform cells. Epidermotropism is more prominent with small intraepidermal clusters (2-3 cells) of lymphocytes. Typical Pautrier microabscesses are seen only in approximately one-third of cases. Subcorneal, intraepidermal and subepidermal bullous formation may result from confluence of Pautrier microabscesses (1460).

**Progression to tumour stage**

With progression from plaque stage to tumour stage the dermal infiltrates become more diffuse, and epidermotropism may be lost. The proportion of tumour cells increase both in number and size, and may include cells with small, medium-sized and large cerebriform nuclei, blast cells with prominent nuclei and intermediate forms. There is a concomitant decrease in the numbers of reactive T-cells and dendritic cells. In approximately 25% of advanced cases, transformation to a CD30 positive or negative large T-cell lymphoma defined by

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**Fig. 4.3** A Plaque-stage mycosis fungoides (MF). B Thick plaque with haemorrhage in MF. C Histopathology of plaque-stage MF. Intra-epidermal and dermal infiltrate.

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**170 Haematolymphoid tumours**
the presence of more than 25% blast cells may be observed.

**Immunoprofile**

The immunophenotypical prototype of MF is CD2+, CD3+, CD4+, CD5+, CD45RO+, CD8, TCR-beta+, CD30-. During progression of the disease loss of CD7, 2 and 5 can occur. Helpful in the diagnosis is the loss of CD7, CD2, CD5, or CD4 in the epidermotropic cerebriform cells. During progression of the disease especially when transformation is present CD4 positive epidermotropic cells can have a cytotoxic phenotype (TIA-1, Granzyme B). In the transformed stage the blast cells can express CD30. Besides the CD4 prototype, a small number of MF cases have a CD8 positive cytotoxic phenotype (TIA-1 and granzyme B). These cases have the same clinical behaviour as the CD4 positive cases.

**Prelymphomatous precursor lesions**

The term “parapsoriasis” is confusing and requires explanation. It encompasses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling lesions (311,312,1375).

Two groups of parapsoriasis can be differentiated (337). The benign form ‘parapsoriasis en plaques’ (Brocq disease), never evolve into malignant lymphoma. The large plaque forms (LPP) with poikiloderma (prereticulotic poikiloderma, parapsoriasis en grandes plaques poikilodermites, poikiloderma vasculare atrophicans, parapsoriasis lichenoides, parakeratosis variegata) or without poikiloderma (parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples), may after several decades evolve into mycosis fungoides or CTCL in up to 10-50% of cases. Few large (more than 5 cm in diameter) patches show pityriasisiform scaling with (poikilodermatous variant) or without telangiectasia and netlike pigmentation. There is no palpable infiltration. Histologically lesions in large plaque parapsoriasis (LPP) are different from MF or other CTCL. Under patchy parakeratosis there is slight atrophy of the epidermis, due to loss of rete ridges. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, spar-
ing the papillary region. There is no significant epidermotropism as usually seen in early stages of mycosis fungoides. The poikilodermatous variant of the diseases in addition shows dilated blood vessels in the upper dermis. T-cell receptor gamma gene rearrangement, which is clonal in about half of the patients with LPP, is without any prognostic significance (2186). There is no significant difference between the observed and expected survivals in patients with LPP.

Histogenesis
Mature skin homing T cells that express the cutaneous lymphocyte antigen (CLA) enable them to specifically home into the skin. Functionally, the neoplastic cells in MF express TH2 phenotype, which accounts for many systemic changes associated with MF due to the production of a TH2-specific cytokine pattern (IL-4, IL-5, IL-10) leading to fever, oedema, eosinophilia, increase of IgE or IgA, and impaired delayed type reactivity (656,2445).

Somatic genetics
There have been a few reports on familial occurrence of MF or CTCL (2160) and on a possible association of HLA-DR5 with MF (2004). HLA class II susceptibility alleles, i.e. HLA-DRB1*11, HLA-DQB1*03 and HLA-DRB1*1104 are more prevalent among patients with MF and are likely to be important in the pathogenesis of MF (1039,1118). T-cell receptor beta and gamma chain genes are clonally rearranged. In advanced cases with extracutaneous involvement, the same clone is usually detected in the skin and in the extracutaneous lesions. In transformed cases the same clone is present in the pre-existing lesions and the high-grade lymphoma (207). In advanced stage, the rate of chromosomal aberrations, especially of chromosomes 1, 6 and 11, increase with the activity of the disease and has prognostic significance in patients with MF. Aberrations of chromosomes 8 and 17 are especially associated with active or progressive disease.

Chromosomal abnormality possibly results in increased genetic instability as a basic prerequisite for the development of CTCL. In G-banding studies, numerical aberrations of chromosomes 6, 13, 15, and 17, marker chromosomes, and structural aberrations of chromosomes 3, 9, and 13 were increased in MF (1209). In contrast to nodal lymphomas, the large cell transformation in cutaneous T-cell lymphoma (CTCL) is not associated with t(2;5)(p23;q35) chromosomal translocation (613,1420). Increased expression of C-myc, p62, TP53 and proliferation markers (PCNA) has been found in advanced stages of MF as compared to early stages of MF suggesting a relationship between levels of these proteins and aggressiveness of CTCL (1192).

Prognosis and predictive factors
The majority of MF patients show an indolent clinical course over years or decades. The prognosis of the disease is defined by its stage. Patients with early
stages, i.e. with patches or thin plaques, without involvement of lymph nodes, peripheral blood or other extracutaneous compartment have an excellent prognosis with survival similar to that of an age, sex, and race-matched population (2575).

Advanced stage and age above 60 years of age indicate a poor prognosis. When extracutaneous involvement or transformation into high-grade lymphoma occurs, expected survival is usually less than one year (2367, 2412).

**Variants**
Apart from the classical form of MF, there are several variants of this disease with unusual or atypical clinical and/or histopathological features. These comprise follicular, bullous, dyshidrotic, granulomatous, hypopigmented, poikilodermic, hyperpigmented, pigmented purpur-
possibly due to an increased expression of skin-selective homing receptors and adhesion molecules in the follicular epithelium (1805). A recent study has demonstrated that follicular MF shows a more aggressive behaviour and a worse prognosis than classical MF (829,2411).

**Granulomatous MF**

Granulomatous MF is characterized by the histological presence of a granulomatous reaction (584), sometimes featuring a sarcoidal or granuloma annulare-like pattern. Multinucleated giant cells may be present (1387). The prognostic and clinical significance of a granulomatous reaction in MF remains uncertain (454).

**Fig. 4.11** Proliferative lymphoid infiltrate in follicular mycosis fungoides (MF).

**Fig. 4.12** Granulomatous MF. Granulomatous plaques with ulceration on the leg.

**Fig. 4.13** Granulomatous mycosis fungoides (MF) with sarcoidal infiltrate pattern.
Sézary syndrome

Definition
Sézary syndrome (SS) is a rare variant of cutaneous T-cell lymphoma (CTCL), characterized by erythroderma, blood involvement and a poor prognosis. Neoplastic lymphocytes are typically mature T-helper cells with cerebriform nuclei. Criteria for the diagnosis of SS include the demonstration of a peripheral blood T-cell clone by molecular or cytogenetic methods; an expanded CD4+ population resulting in a CD4:CD8 ratio > 10, and immunophenotypic abnormalities such as absent expression of T-cell antigens (CD2, CD3, CD4 and/or CD5). Sézary syndrome (SS) is part of a broader disease spectrum, erythrodermic CTCL. The presence of a clonal T-cell population in the peripheral blood distinguishes SS from reactive disorders that exhibit erythroderma and circulating cells with cerebriform nuclei (pseudo-SS) (777).

ICD-O code 9701 / 3

Epidemiology
Sézary syndrome accounts for less than 5% of all cutaneous T-cell lymphomas (2523). It occurs almost exclusively in adults, characteristically presents over the age of 60 and has a male predominance (2523).

Etiology
SS is of unknown etiology. However, a syndrome clinically indistinguishable from SS is occasionally seen in HTLV-1 associated lymphoma/leukaemia.

Clinical features
SS comprises a clinical triad of pruritus, erythroderma and lymphadenopathy. The pruritus is commonly intractable and sufficiently severe to prevent the patient sleeping or pursuing a normal life. Additional clinical features include alopecia, ectropion, nail dystrophy, palmo-plantar keratoderma and leonine facies. Bacterial skin infection is common in Sézary patients and may lead to a marked deterioration in their cutaneous disease. An increased prevalence of secondary malignancies, both cutaneous and systemic, has been reported in SS and attributed to the immunoparesis associated with loss of normal circulating CD4 cells (2075).

Tumour spread and staging
Haematological involvement was defined in the TNM classification of MF as more than 5% atypical circulating lymphocytes (B1), but was not included as part of the Bunn-Lamberg staging system (1356). Sézary patients are all T4/B1 (erythroderma with blood involvement) but staging will vary from stage III if there is no lymph node involvement to IVB if there is bone marrow involvement. In practice, most cases of SS are staged as IVA. In 1988, the definition of B1 was increased from 5 to 20%, by the NCI, but was still not included as part of the staging system (2071).

The problem is that erythrodermic CTCL represents a spectrum and that any attempt to distinguish SS from cases that show a lesser degree of haematological involvement is necessarily arbitrary. An alternative approach is to develop a staging system that incorporates both lymph node status and haematological stage. A haematological staging system

Fig. 4.14 Erythroderma and scaling of the face in Sézary syndrome.

Fig. 4.15 Palmar hyperkeratosis and onychodystrophy in Sézary syndrome.

Fig. 4.16 Sézary syndrome. Note erythroderma, oedema of the skin, and swelling of lymph nodes.
comprising five categories (H0-H4) was proposed by Russell-Jones and Whittaker (1998), and subsequent data showed an increase in disease-specific death rates for each category with the most significant change occurring at H2, defined by 5% Sézary cells with a T cell clone demonstrated by PCR, or a T cell clone demonstrated by Southern blot analysis only (2077). The need for a haematological staging system has also been recognised by the International Society for Cutaneous Lymphoma ISCL (2444). Currently this is being tested in a larger, multi-centre study under the auspices of the ISCL.

**Histopathology**

Despite minor differences (1099), the range of histological changes in SS are not dissimilar to those seen in patients with mycosis fungoides (2135). Epidermotropism is a variable feature, and the size of Sézary cells varies in the skin as it does in blood. Only 2/3 of the skin biopsies and 73% of patients had diagnostic changes in the skin biopsies. Other causes of erythroderma need to be differentiated from SS, particularly drug induced erythroderma and chronic actinic reticuloid, both of which may show a high proportion of activated lymphocytes with cerebriform nuclei (2135). In cases with a non-specific histology, the differential diagnosis would include other causes of erythroderma such as eczema or psoriasis.

**Immunoprofile**

A typical Sézary cell is a mature helper T cell with a memory phenotype. A classic immunoprofile is CD2, CD3, CD4, CD5, CD45RO positive and CD8 negative (1368,2526). The majority of Sézary cells are also CLA positive (1827) and CD7 negative, and this latter feature has been proposed as a method of distinguishing Sézary cells from normal lymphocytes (957). However, further studies have shown that the neoplastic cell population is present in both the CD7 positive and CD7 negative subset in the same patient (657). More recently, Bernengo et al have demonstrated that CD4 positive Sézary cells typically loose the CD26 marker and that a diagnosis of SS or MF with haematological involvement can be made if the CD26 negative subset exceeds 30% of the CD4 positive cells (215).

Complete loss of T cell antigens such as CD2, CD3, CD4, or CD5 is present in approximately 2/3 of patients with SS (957). An alternative approach would be the identification of a tumour-specific antigen (669). Recently two differentiation antigens P140 and SCS have been reported in circulating Sézary cells and P140 was also found in skin-infiltrating cells of patients with SS (1715).
Histogenesis
The postulated cell of origin is a mature peripheral T cell which has skin-homing properties and exhibits a helper-cell phenotype.

Somatic genetics
Recurrent chromosomal translocations have not been detected in Sézary syndrome, but complex clonal numerical and structural chromosomal abnormalities are common and associated with a poor prognosis (1505,2343). M-FISH techniques have shown a high rate of unbalanced translocations and associated deletions often involving chromosomes 1p, 10q, 14 and 15 (1505). CGH studies have identified a consistent pattern of chromosomal gains/deletions (1p, 10q, 13q, 19, 17p losses and 4/4q, 17q and 18 gains) which, with the exception of 17q gains in Sézary syndrome, are identical to mycosis fungoides suggesting a similar pathogenesis (1210,1504). Allelic losses on 1p, 9p, 10q and 17p have been confirmed by LOH studies and a high rate of microsatellite instability (MSI) has also been detected (2079, 2080). These findings suggest that dysregulated genes at these chromosomal loci are involved in the pathogenesis (1554,2078). There is a high rate of genomic instability as indicated by the presence of chromosomal instability (1505). Constitutive activation of Stat 3 and chromosomal amplification of JUNB, a member of the AP-1 transcription factor complex, have been identified in Sézary syndrome (1089,1506). A recent cDNA array study in Sézary syndrome has confirmed the presence of JUNB over-expression and has also revealed over-expression of other genes associated with a TH2 phenotype such as Gata-3 and RhoB (1211). These array findings appear to allow the identification of a poor prognostic group (1211).

Prognosis and predictive factors
Sézary syndrome has a poor prognosis with a median survival of 2 to 4 years depending on the exact definition used (777,1271,2044,2523). Absolute Sézary cell count and lymph node involvement are independent prognostic factors. In addition, large cell transformation and the development of skin tumours on a background of erythroderma are poor prognostic signs.

Fig. 4.20 Diagnostic pathways for the differential diagnosis of erythroderma. Algorithm for the evaluation and diagnosis of erythroderma due to cutaneous T-cell lymphoma (E-CTCL) vs. 'reactive' causes of erythroderma. TCR, T-cell receptor. *A CD4/CD8 ratio >10 or an absolute Sézary cell count of 1 10^9 L^{-1} have been proposed as diagnostic criteria for Sézary syndrome (SS), but this algorithm requires additional immunophenotypic or genotypic data. Even so, a Sézary cell count > 1 10^9 L^{-1} or a CD4/CD8 ratio > 10 increases the probability of neoplasia, and separates SS from E-CTCL with a lesser degree of blood involvement. **Abnormal T-cell immunophenotype = an increased population of CD4+ cells that are CD26 > 30% or p140+. CD7 is less reliable. Aberrant T-cell immunophenotype = loss of pan T-cell markers such as CD2, CD3 or CD5, and/or double-negative T cells (CD4 and CD8). In skin, the loss of CD7 from epidermal lymphocytes is CTCL specific. From: R. Russell-Jones (1997).
Granulomatous slack skin (GSS) is clinically characterized by the development of bulky skin lesions in the major skin folds and histologically by a granulomatous infiltrate composed of small lymphocytes and scattered multinucleated giant cells containing nuclei arranged in a wreath-like fashion.

**Synonyms**
Progressive atrophying chronic granulomatous dermohypodermitis

**Epidemiology**
GSS is a rare form of primary cutaneous T-cell lymphoma. GSS usually appears in the third or fourth decade, but can also affect children. GSS occurs almost exclusively in Whites. The male to female ratio is 2:1 to 3:1.

**Clinical features**
GSS begins with slightly infiltrated, poikilodermatous sharply demarcated patches and plaques. Predilection sites are the intertriginous areas, especially the axillary and inguinal folds. After years, pathognomonic bulky pendulous skin folds develop as a result of progressive destruction of elastic fibres. The lesions then resemble cutis laxa. Occasionally ulceration occurs. Regional lymphadenopathy may be present. In contrast to granulomatous MF, GSS is in almost all cases confined to intertriginous areas, and runs a more benign course than classic MF.

**Histopathology**
Early lesions of GSS display a bandlike infiltrate of small lymphocytes without significant nuclear atypia. More advanced lesions show a dense lymphocytic infiltrate throughout the entire dermis. Nuclear atypia of lymphocytes is less pronounced than in granulomatous MF. The diagnostic hallmark is numerous multinucleated histiocytic giant cells, which are scattered throughout the background of the dense lymphocytic infiltrate. These giant cells contain 20-30 nuclei located at the periphery of the cytoplasm. Elastophagocytosis and emperipolesis (phagocytosis of lymphoid cells by giant cells) are present. Elastic stains demonstrate the loss of elastic fibres at the sites of the infiltrates in all dermal layers. On occasion, involvement of large vessels occurs. Ultrastructurally, the lymphocytes show hyperchromatic cerebriform nuclei similar to those seen in mycosis fungoides and Sézary syndrome. Speciﬁc inﬁltration of regional lymph nodes or internal organs exhibiting similar features as in the skin has been observed in rare cases.

**Immunoprofile**
The lymphoid tumour cells display a T helper phenotype with expression of CD3, CD4 and CD45RO. There may be loss of other T-cell markers like CD5 or CD7. In rare cases, the tumour cells express CD30.

**Genetics**
Clonal rearrangement of TCR genes can be found in most cases and is a useful diagnostic tool in early stages of the disease. Trisomy 8 has been reported in two cases.

**Histogenesis**
The tumour cells represent skin-homing T-helper cells.

**Prognosis and predictive factors**
The disease has a long natural history with a slowly progressive course over decades. Occasionally involvement of regional lymph nodes is found, but does not seem to affect survival. Although life expectancy is not reduced by GSS per se, other cutaneous and nodal lymphomas such as mycosis fungoides, Hodgkin lymphoma and peripheral T-cell lymphomas occur in approximately 20 – 50% of the patients, often years or even decades after the manifestation of GSS.
CD30-positive T-cell lymphoproliferative disorders (LPD) of the skin (CD30+LPD) represent a distinctive group of primary cutaneous T-cell lymphoma. The spectrum of CD30+ LPD includes lymphomatoid papulosis (LyP), primary cutaneous anaplastic lymphoma (C-ALCL) and borderline cases which differ in their clinical and histological presentations (191, 1174,1225,1795,2520). A feature common to all is the expression of CD30, a cytokine receptor belonging to the tumour necrosis factor receptor superfamily.

The term 'borderline lesions' has been applied to lesions that show clinical presentation of one entity (e.g. C-ALCL) but histological features of another one (e.g. LyP). This discrepancy may result in difficulties to assign such lesions to a distinct entity. Clinical presentation plays a crucial role in such discordant cases.

**Lymphomatoid papulosis (LyP)**

**Definition**

LyP is a chronic recurrent lymphoproliferative skin disease with self-regressing papulo-nodular skin lesions and atypical lymphoid cells in a polymorphous inflammatory background (1466).

**ICD-O code**

9718/1

**Epidemiology**

LyP is a rare disease with an estimated prevalence of 0.1 to 0.2 cases per 100 000 and a male to female ratio of 1.5:1 (2456). Mostly people in the third and fifth decades are affected, but children can also be involved.

**Localization**

Although no definite predilection site has been identified, LyP lesions more often arise on the trunk, especially the buttocks, and extremities.

**Etiology**

The cause of the disease is unknown. Endogenous retroviral elements have been identified in LyP lesions (1242). Interaction of CD30 and CD30L as well as TGF-beta and its receptor play an important role in growth regulation, including regression of tumoural lesions (1177,1648).

**Clinical features**

LyP is characterized by grouped or disseminated asymptomatic papules and/or nodules, which regress spontaneously after a few weeks sometimes leaving behind varioliform scars (1174). Often new lesions develop concurrently in the same or another body region. Larger nodules up to 2 cm can develop and persist for months (2524). Clinicopathologic variants of LyP include regional follicular and pustular forms (2076).

**Histopathology**

The histological features of LyP are variable and depend on the stage of the lesions and disease. Three histologic subtypes (types A, B and C) have been delineated (2524) which represent a spectrum with overlapping features (2148). In fully developed LyP lesions, there is a wedge-shaped diffuse dermal infiltrate which contains medium-sized to large pleomorphic or anaplastic lymphoid cells with irregular nuclei, sparse chromatin and mitotic activity. Some of the large atypical lymphoid cells resemble Reed-Sternberg cells. Ulceration may be present. In type A lesions, scat-
tered tumour cells are intermingled with numerous inflammatory cells such as neutrophils, eosinophils and histiocytes. Type C lesions show cohesive sheets of large atypical lymphoid cells with only a few intermingled reactive inflammatory cells. The rare type B is characterized by an epidermotropic infiltrate of small atypical lymphoid cells with cerebriform nuclei and histologically resembles mycosis fungoides. Various histologic types may be present in individual patients at the same time. Due to an overlap of histologic features between LyP and primary as well as secondary cutaneous ALCL, final diagnosis depends on correlation of clinical presentation and histologic findings.

Immunohistochemistry
A hallmark of the large atypical lymphoid cells is their positivity for CD30 (1173, 1227). The large atypical lymphoid cells in LyP are of T-cell origin with a CD3+, CD4+, CD8-. In 10% of the cases tumour cells express CD56+ (193). Usually CD2 and CD5 are expressed, whereas often CD7 and sometimes CD3 are absent. In addition, expression of activation markers such as HLA-DR and CD25 (interleukin 2-receptor) is found. Cytotoxic molecules such as TIA-1 and granzyme B are expressed in 70% of the cases (1342). CD56 is generally negative (968). CD15, a marker for Reed-Sternberg cells in Hodgkin lymphoma, is usually not expressed in LyP. In contrast to the tumour cells expressing CD30 as in LyP type A and type C, the small atypical lymphocytes present in LyP type B are usually negative for CD30.

Genetics
Clonal rearrangement of T cell receptor genes can be found in at least 40% of LyP lesions. Cytogenetic studies have demonstrated chromosomal deletions and rearrangements of chromosomes 1, 7, 9 and 10 (1813). The t(2;5)(p23;q35) translocation is not detected in LyP (613).

Histogenesis
LyP represents a proliferation of activated skin-homing T-cells with a unique cytotoxic phenotype (TIA-1+).

Prognosis and predictive factors
LyP exhibits a favorable prognosis with 5-year-survival rates of 100% (191,1795). So far, there are no data indicating that any kind of therapeutic intervention in LyP alters the natural history of the disease or prevents progression to other malignant lymphomas (650). Other cutaneous and nodal lymphomas such as mycosis fungoides, Hodgkin lymphoma and systemic or cutaneous CD30+ large T-cell lymphoma (LTCL) develop in 5-20% of patients with LyP (191,1174). Long-term follow-up is therefore recommended. These lymphomas are usually referred to as LyP-associated malignant lymphomas. They can develop prior to, concurrent with, or after the manifestation of LyP (1175) and result in a fatal outcome in 2% of patients (191). No risk factors have been identified which definitely indicate likely progression to associated lymphomas in LyP patients. So far, only fascin expression is found at a significantly higher rate in LyP cases associated with systemic lymphomas (1243).

Primary cutaneous anaplastic large-cell lymphoma

Definition
Primary cutaneous anaplastic lymphoma (C-ALCL) is a neoplasm composed of large atypical lymphocytes of either pleomorphic, anaplastic or immunoblastic cytomorphology and expression of the CD30 antigen by the majority, i.e. more than 75% of tumour cells. Primary cutaneous and primary nodal CD30+ ALCL are distinct clinical entities that can have similar morphologic features and some overlap in immunophenotype, but differ in age of onset, genetic features, etiology and prognosis (600,2259,2493).

ICD-O-code 9718/3

Synonyms
Regressing atypical histiocytosis, EORTC: Primary cutaneous large cell T cell lymphoma CD30+

Epidemiology
C-ALCL is the second most common form of cutaneous T-cell lymphoma with an incidence of 0.1-0.2 patients per 100'000. This form of lymphoma affects
mainly people in their sixth decade with a male to female ratio of 2-3:1 (191,1226), but it can also occur in childhood. C-ALCL is a common form of cutaneous T-cell lymphoma in HIV-infected individuals (1248).

Localization
The extremities and head are predilection sites (196,1228).

Clinical features
ALCL usually presents as an asymptomatic, solitary firm nodule which rapidly grows and often ulcerates (1174). Approximately 20% of the patients have multifocal disease, i.e. two or more lesions at multiple anatomic sites (191). Involvement of regional lymph nodes can occur. Other extra-cutaneous spread is rare. If there is no therapeutic intervention, spontaneous regression occurs in 10-40% of the tumour lesions (191,1226).

Histopathology
There is a dense nodular infiltrate extending through all levels of the dermis into the subcutis. Epidermotropism may be found. The infiltrate consists of cohesive sheets of large, cells with irregularly shaped nuclei and one or multiple nucleoli and an abundant, clear or eosinophilic cytoplasm. Mitoses are frequent. Clusters of small reactive lymphocytes are found within and around the tumour. Eosinophils, plasma cells, and accessory dendritic cells usually are not prominent in C-ALCL. Variants of C-ALCL include neutrophil-rich or pyogenic CD30+ ALCL presenting histologically with small aggregations or scattered CD30+ medium to large pleomorphic lymphoid cells within an extensive infiltrate of neutrophils (341,1549).

Immunohistochemistry
C-ALCL displays an activated T-cell phenotype with expression of T-cell associated antigens CD2, CD3, CD4 and CD45RO, activation markers such as CD25 (IL-2R), CD30, CD71 and HLA-DR, and frequent expression of cytotoxic molecules such as TIA-1, granzyme B and perforin (290,1342). CD30 must be expressed by at least 75% of the large pleomorphic or anaplastic lymphoid cells. Variable loss of T cell antigens (CD2, CD3, CD5 and CD7) can be found (1228). In contrast to systemic (nodal) ALCL, C-ALCL does not express EMA, but may express the cutaneous lymphocyte antigen (CLA, HECA-452) and homeobox gene HOXC5 (243). C-ALCL is consistently negative for the anaplastic lymphoma related tyrosine kinase (ALK).

Genetics
Clonal rearrangement of T cell receptor genes is detected by Southern blot and PCR in most cases (over 90%) of C-ALCL (1467). The translocation t(2;5) (p23;q35) resulting in expression of npm-alk protein (p80), which is a characteristic feature of systemic anaplastic large cell lymphomas, is rarely if ever found in C-ALCL (228,613). Systemic ALCL may present with cutaneous disease, and the identification of ALK-expression is helpful in this distinction.

Histogenesis
Activated skin-homing T-cell.

Prognosis and predictive factors
C-ALCL has a favourable prognosis with 5 year-survival rates of 90% (191,1795). Up to 40% of C-ALCL show spontaneous regression (198). Regional lymph nodes may be involved, but the survival rate is similar to patients with skin lesions only (191). Other extracutaneous spread occurs in 10% of the patients, especially in those with multiple grouped or multifocal tumour lesions with a fatal outcome in only a minority of the patients (191). Spontaneous regression and age less than 60 years are associated with a better prognosis, while extracutaneous disease and higher age tend to have a worse outcome. Cytomorphology (anaplastic or pleomorphic and immunoblastic) seems not to be a prognostic factor (191,1795).
Subcutaneous panniculitis-like T-cell lymphoma

Definition
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a T-cell lymphoma with preferential infiltration of subcutaneous tissue by atypical lymphoid cells of varying size, often with marked tumour necrosis and karyorrhexis.

ICD-O code 9708/3

Historical annotation
In the historical literature, most cases of SPTCL were probably diagnosed as histiocytic cytophagic panniculitis [562, 1527].

Epidemiology
Subcutaneous panniculitis-like T-cell lymphoma is a rare form of lymphoma, representing less than 1% of all non-Hodgkin lymphomas. It occurs in males and females equally, and has a broad age range. Cases have been reported in children under the age of two years. Most cases occur in adults [1060, 1341, 2026, 2480].

Etiology
Unknown. In most patients the disease presents sporadically.

Localization
Patients present with multiple subcutaneous nodules, usually in the absence of other sites of disease. The most common sites of localization are the extremities and trunk.

Clinical features
Clinical symptoms are primarily related to the subcutaneous nodules. The nodules range in size from 0.5 cm to several cm in diameter. Larger nodules may become necrotic, but ulceration of cutaneous lesions is rare. Systemic symptoms, most commonly fever, are variable but usually present. Some patients may present with a haemophagocytic syndrome with pancytopenias, fever, and hepatosplenomegaly [338, 863, 2480]. Lymphadenopathy is usually absent.

Histopathology
The infiltrate extends diffusely through the subcutaneous tissue, usually without sparing of septae. The overlying dermis and epidermis are typically uninvolved. The neoplastic cells range in size from small cells with round nuclei and inconspicuous nucleoli to larger transformed cells with hyperchromatic nuclei. The lymphoid cells have a moderate amount of pale-staining cytoplasm. A helpful diagnostic feature is the rimming of the neoplastic cells surrounding individual fat cells [1341]. Admixed reactive histiocytes are frequently present, particularly in areas of fat infiltration and destruction. The histiocytes are frequently vacuolated, due to ingested lipid material. Vascular invasion may be seen in some cases, and necrosis and karyorrhexis are common. However, the infiltrates usually are confined to the subcutaneous tissue, with sparing of the dermis. This feature is helpful in the differential diagnosis from other lymphomas involving skin and subcutaneous tissue. The necrosis is primarily apoptotic in nature, possibly related to the release of cytotoxic molecules [1341, 2133]. Cutaneous γδ T-cell lymphomas can have a panniculitis-like component, but commonly show both dermal and epidermal involvement in addition to subcutaneous disease [1060, 1341, 2026, 2366]. Plasma cells and reactive lymphoid follicles are generally absent, in contrast to lupus profundus panniculitis, and other forms of lobular panniculitis. In some cases of SPTCL the infiltrates in initial phases may appear deceptively benign, and the differential diagnosis with benign panniculitis may be difficult [338, 863].

Immunoprofile
SPTCL is derived from αβ cells, T-cells with a cytotoxic profile. The cells are usu-

Fig. 4.28 Subcutaneous panniculitis-like T-cell lymphoma (SPTCL). A Erythematous plaques and nodules on the leg with ulceration. B Diffuse infiltration of subcutaneous tissue simulating lobular panniculitis. Large atypical cells rimming around fat lobules.
ally CD8-positive, with expression of cytotoxic molecules including granzyme B, perforin, and T-cell intracellular antigen (TIA-1) \cite{1341,2026}. However, in contrast to other cytotoxic TCLs related to the innate immune system (enteropathy-type T-cell lymphoma, extranodal NK/T-cell lymphoma), the cells are negative for granzyme M (metase) \cite{694,1122,1325,2564}. The neoplastic cells are capable of producing a number of cytokines and chemokines, a feature that is related to development of systemic symptoms and the haemophagocytic syndrome \cite{338,2340}. Cutaneous γδ T-cell lymphomas \cite{119,338,1341,2026} are distinguished from SPTCL, even if a panniculitis-like component is present.

**Histogenesis**
Mature cytotoxic T-cell of the adaptive immune system.

**Precursor lesions**
Oligoclonal T-cell populations may be found in some cases of lobular panniculitis, suggesting the potential for clonal evolution in rare cases \cite{1484}. However, progression from cytophagic panniculitis without monoclonality to SPTCL rarely if ever occurs \cite{1527}.

**Somatic genetics**
The neoplastic cells show rearrangement of T-cell receptor genes, and are negative for Epstein Barr sequences.

**Prognosis and predictive factors**
Dissemination to lymph nodes and other organs is uncommon and usually occurs late in the clinical course. The natural history is often aggressive \cite{694,863,917,1300,2026}. A haemophagocytic syndrome is a frequent complication in αβ cases and usually precipitates a fulminating downhill clinical course. However, if therapy for the underlying lymphoma is instituted and is successful, the haemophagocytic syndrome may remit.
Primary cutaneous peripheral T-cell lymphoma, unspecified

Definition
A heterogeneous group of cutaneous T-cell lymphomas that do not fit into one of the well-defined subtypes of T-cell lymphoma/leukaemia. Three provisional entities have been separated: Cutaneous γδ T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma and primary cutaneous small-medium CD4+ T-cell lymphoma.

ICD-O code 9709/3

Synonyms and historical annotation
The category of the peripheral T-cell lymphomas, unspecified (PTL) was introduced in the REAL classification (960) and was maintained in the WHO classification (1369). It encompasses per definition all T-cell neoplasms that do not fit into any of the better defined subtypes of T-cell lymphoma/leukaemia. As such it constitutes a heterogeneous group of diseases. These conditions are most frequently systemic (1121). Primary cutaneous PTL are rare and constitute less than 10% of all cutaneous T-cell lymphomas (CTCL) in large series (195). They correspond to the CD30-negative CTCL in the EORTC classification and show an aggressive behaviour in most cases (195,2523). Therefore, distinction between "primary" and "secondary" cutaneous involvement seems less important for this category. Although it is still controversial how these tumours can be grouped into separate diseases, recent investigations have suggested that some disorders within this broad group of neoplasms can now be separated out as provisional entities. For the remaining diseases that do not fit into either of these provisional entities (Table 4.1), the designation PTL, unspecified, is maintained.

Cutaneous γδ T-cell lymphoma

Definition
Cutaneous γδ T-cell lymphoma (CGD-TCL) is a lymphoma composed of a clonal proliferation of mature, activated γδ T-cells expressing a cytotoxic phenotype. This group includes cases of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with a gamma/delta phenotype. In the WHO classification 2001, these were grouped together with SPTCL of αβ origin (1121), but they show distinctive features and seem to be more closely related to other CGD-TCL (192,1060,1533,2026,2366). A similar and possibly related condition may present primarily in mucosal sites (98). Whether cutaneous and mucosal γδ TCLs are all part of a single disease, i.e. muco-cutaneous γδ TCL, is not yet clear (1122,2539).

Epidemiology
CGD-TCLs are rare, with approximately 50 cases reported (1533,1665,2366). In one series they represented <5% of cutaneous T-cell lymphomas (1879). Most cases occur in adults. There is no reported sex predilection.
Etiology
The distribution of disease reflects the localization of normal γδ T cells, which are believed to play a role in host mucosal and epithelial immune responses (268). Impaired immune function associated with chronic antigen stimulation may predispose to the development of mucosal and CGD-TCLs (98,2539). Epstein-Barr virus (EBV) is generally negative in CGD-TCLs, but may be positive in primary γδ TCL in mucosal sites (98,1191,2366,2539).

Clinical features
The clinical presentation is variable. The disease may be predominantly epidermotropic and present with patches/plaques, or it may be predominantly motropic and present with patches/disease may be predominantly epidermotropic in primary CGD-TCL {98,119}. Impaired immune function associated with chronic antigen stimulation may predispose to the development of mucosal and CGD-TCLs {98,2539}. EBV is generally negative in primary CGD-TCL {98,2539}. May predispose to the development of cutaneous γδ T-cell lymphoma.

Histopathology
The neoplastic cells are generally medium to large in size with coarsely clumped chromatin (2366). Large granular lymphocytes with vesicular nuclei and prominent nucleoli are infrequent. Apoptosis and necrosis are common, often with angioinvasion (1533). Three major histologic patterns of involvement are present: epidermotropic, dermal, and subcutaneous. However, usually more than one histologic pattern is present in the same patient in different biopsy specimens or within a single biopsy specimen (2366). Epidermal infiltration may occur as mild epidermotropism to marked pagetoid reticulosis-like infiltrates (221,1665,1879). Subcutaneous nodules may be panniculitis-like or more solid in appearance and may show rimming of fat cells, similar to SPTCL of αβ origin (1533). Dermal and epidermal involvement often coexists with subcutaneous disease, in contrast to SPTCL of γδ origin, which is mainly or exclusively subcutaneous in distribution (192,1060,2026).

Immunoprofile
The cells are CD3+, CD2+, CD7 +/-, but usually negative for CD5 (2539). Most CGD-TCLs lack both CD4 and CD8, but some are CD8+ (2366). The cells are positive for TCR-δ, but lack βF1 of the γδ T-cell receptor. The absence of βF1 may be used to infer a γδ origin under appropriate circumstances (1151,2026,2365). The cells are positive for TIA-1 and the cytotoxic proteins granzyme B, granzyme M, and perforin. {1325,1341,1533}. CD56 is frequently expressed (1533).

Histogenesis
Functionally mature and activated cytotoxic γδ T-cells of the innate immune system.

Somatic genetics
The cells show clonal rearrangement of the TCR gamma gene. TCR beta may be rearranged or deleted, but is not expressed. Cases with predominant subcutaneous involvement express Vδ2, but this has not been studied in other CGD-TCL (1860,2026). EBV is generally negative in primary CGD-TCL (98,119).

Prognosis and predictive factors
Patients have aggressive disease resistant to multiagent chemotherapy and/or radiation (1665,2366). In a recent series of 33 patients, 22 (66%) died within 5 years of diagnosis, and in the same study TCRδ1 expression was an independent predictor of survival (2366). Among 33 patients with CGD-TCL, there was a trend for decreased survival for patients who had subcutaneous fat involvement in comparison with patients who had epidermotropic or dermal disease only. Age, sex, and lymphadenopathy did not have any discernible prognostic impact (2366).

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Definition
A cutaneous T-cell lymphoma characterized by epidermotropic infiltrates of CD8-positive, cytotoxic T-cells of γδ origin. The behaviour is aggressive in most cases (223).

Epidemiology
This disease occurs mainly in adults and is rare with approximately 30 cases published worldwide (36,192,223,1533,2062).

Clinical features
The clinical presentation is characterized by sudden eruptions of localized or disseminated papules, nodules and tumors, often with central ulceration and necrosis. Superficial, hyperkeratotic patches and plaques may also be present (36,223). The disease may resemble epidermotropic variants of other cutaneous T-cell lymphomas and is similar, if not identical to cases described as generalized pagetoid reticulosis of the Ketron-Goodman type (1252,1533). Classical MF, which may express CD8 in rare cases (1456,1880,2062,2510), usu-
ally does not show overt destruction and necrosis and has a more protracted behaviour with progression over years from patches to plaques and tumours. The disease may disseminate to other visceral sites (lung, testis, central nervous system, oral mucosa), but lymph nodes are often spared (223).

**Histopathology**

The histological and cytological appearance is very variable ranging from a lichenoid pattern with marked, pagetoid epidermotropism and subepidermal edema to deeper, more nodular infiltrates. The epidermis may be acanthotic or atrophic, often with necrosis, ulceration and blister formation (36,223). Invasion and destruction of adnexal skin structures are commonly seen (1533). Angiocentricity and angioinvasion may be present (1533). Tumour cells are small-medium or medium-large with pleomorphic or blastic nuclei (223).

**Immunoprofile**

By definition these lymphomas have a CD3+, CD4+, CD8-, CD30- phenotype sometimes with loss of pan T-cell markers (195,783). Cytotoxic proteins are generally not expressed (195).

**Histogenesis**

Skin homing, CD4-positive T-cell.

**Somatic genetics**

The TCR genes are clonally rearranged (783,878). Demonstration of clonality is a useful criterion for distinction from pseudo-T-cell lymphomas, which may also present with a solitary plaque or nodule. No consistent cytogenetic abnormalities have yet been identified.

**Prognosis and predictive factors**

These lymphomas have a rather favourable prognosis with an estimated 5-year survival of 60-80% (195,783,878,2267). Cases presenting with solitary or localized skin lesions seem to have an especially favourable prognosis (195,878).

**Primary cutaneous PTL, unspecified**

Definition

The designation PTL, unspecified is maintained for cutaneous T-cell lymphomas that do not fit into any other category. These lymphomas have a rather favourable prognosis with an estimated 5-year survival of 60-80% (195,783,878,2267).

**Histopathology**

These lymphomas show dense, diffuse or nodular infiltrates within the dermis with tendency to infiltrate the subcutis.
phomas that originate from mature, transformed T-lymphocytes and that do not fit into any of the better defined subtypes of mature cutaneous T-cell neoplasms. Hence, other categories of T-cell lymphoma must be excluded. These include the 3 provisional entities described above. Furthermore, given the wide variety of histologic appearances of tumour stage mycosis fungoides (MF), a diagnosis of MF should always be ruled out by complete clinical examination and an accurate clinical history.

**Epidemiology**
These tumours account for 5 to 10% of all primary cutaneous T cell or NK cell lymphomas (195). All ages may be affected, but the disease is most common in adults.

**Clinical features**
Most lymphomas in this category present with rapidly growing tumours or nodules that may be multiple or (more rarely) solitary or localized (195,197,878,2523). No sites of predilection have been recorded.

**Histopathology**
Skin infiltrates are most often diffuse, but nodular or band-like patterns can be seen. Epidermotropism is mild or absent in most cases. The tumour cells are medium to large, usually with markedly pleomorphic nuclei. Rare cases may show a predominance of cells that are more immunoblastic in appearance (197,2523). Small reactive lymphocytes, eosinophils and plasma cells may be present (195), but the inflammatory background is usually not as pronounced as it can be in nodal malignancies.

**Immunoprofile**
The tumour cells express T-cell associated antigens (CD2, CD3, CD5), but usually lack CD7; most cases are CD4+, but rare tumours may be CD8+ or positive (or negative) for both CD4 and CD8 (195). Cytotoxic antigens (TIA-1+, granzyme B) are usually not expressed (195). Occasional tumour cells may be CD30-positive.

**Histogenesis**
Skin homing T-cells.

**Precursor lesion**
There are no known precursor lesions. As mentioned, cases of transformed MF may closely resemble peripheral T cell lymphoma unspecified and can only be distinguished on clinical grounds.

**Somatic genetics**
The TCR genes are clonally rearranged. No consistent cytogenetic abnormalities have yet been identified.

**Prognosis and predictive factors**
The prognosis is poor with 5-year survival rates of less than 20% (195,878). Cases with immunoblastic morphology may have an even more aggressive behaviour (197,2523). Cases with solitary/localized lesions seem to behave just as aggressively as those with multiple lesions (195).
Fig. 4.37 Primary cutaneous peripheral T-cell lymphoma, unspecified. A Grouped and B disseminated skin lesions. C The dermal neoplastic infiltrate is dense and D consists of large, pleomorphic cells with irregular nuclei and numerous mitoses.
Definition
Adult T cell leukaemia / lymphoma (ATLL) is a malignancy of mature CD4+ T cells caused by the human T-cell leukaemia virus type I (HTLV-1).

ICD-O code 9827/3

Synonyms
Adult T-cell leukaemia (ATL)

Epidemiology
ATLL is endemic in some regions of the world, especially in southwest Japan, the Caribbean islands, South America, and parts of Central Africa (1848,2392).

Etiology
ATLL develops in 1% to 5% of individuals infected with HTLV-1 after more than 2 decades of viral persistence. In most patients viral exposure occurs early in life, and incidence figures are related to the place of birth, not residence. HTLV-1 proviral DNA is monoclonally integrated in the malignant T cell. HTLV-1 encodes the transcriptional activator Tax, which can transform T cells by increasing the expression of a unique set of cellular genes involved in T cell proliferation (1589).

Localization
Based on organ involvement and severity, ATLL is divided into four clinical categories: acute, chronic, lymphoma, and smoldering types (2171). Cutaneous involvement is seen in up to 50% of patients. Lymph nodes, liver and spleen are frequently involved.

Clinical features
Patients with ATLL exhibit various cutaneous manifestations. The most frequent manifestation is nodules/tumours (33.9%), followed by red papules (22.6%), erythematous plaques (19.4%) and macules (6.5%) (2142). Nodules/tumours usually occur as solitary or several lesions on limited sites, whereas multiple papules tend to be distributed over large areas of the body. Subcutaneous tumours (4.8%), erythroderma (3.5%), and purpura (1.6%) are less frequent, and alopecia, folliculitis, erythema multiforme, and prurigo are rarely seen. In addition to the four clinical types, the cutaneous type of ATLL has been proposed to indicate skin-limited lesions without lymph node involvement or leukaemic involvement (1144). ATLL limited to the skin may be considered part of the smouldering type. Two patterns of skin involvement are seen; i.e., tumoural and erythematopapular. The tumoural subtype has been reported to have a worse prognosis than the erythematopapular one.

Histopathology
Individual skin lesions of ATLL exhibit varying degrees of tumour cell infiltration from the epidermis to subcutaneous tissue. Epidermotropism of the malignant T cells is present in the majority of cases,
and even Pautrier microabscesses, indistinguishable from those of mycosis fungoides and Sézary syndrome, are often seen. The cells have medium- to large-sized pleomorphic nuclei, and occasionally show mitoses. Nuclear irregularity may be marked, with polylolated flower cells often seen in the blood and tissues. Eosinophils may be intermingled with lymphocytes. In some cases, the tumour cells infiltrate mainly in the subcutaneous tissue (2142,2171).

**Immunohistochemistry**

In general, the malignant T cells are positive for CD3, CD4, CD25, and CD45RO but negative for CD7, CD8, CD19, and CD20 (2171). CD30 expression may be seen in larger transformed cells.

**Prognosis and prognostic factors**

The prognosis of ATLL patients with skin lesions is dependent on clinical and histological factors, and relates to the four main clinical subtypes. It has been suggested that cases of the smoldering type of ATLL have a poorer prognosis if there are deep dermal cutaneous infiltrates, as compared to cases in which skin manifestations are absent, or only present as superficial infiltration (2142).

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Fig. 4.39 Adult T-cell leukaemia/lymphoma (ATLL). **A** Erythematous macule, showing infiltration of atypical lymphocytes in the upper dermis with Pautrier microabscess. **B** Tumour, massive infiltration of pleomorphic lymphocytes in the dermis.
Extranodal NK/T-cell lymphoma, nasal-type

Definition
Extranodal NK/T-cell lymphoma, nasal-type, is an EBV+, nearly always extranodal lymphoma of small, medium or large cells usually with an NK-cell, or more rarely cytotoxic T-cell phenotype. The skin is the second most common site of involvement after the nasal cavity/nasopharynx, and skin involvement may be a primary or secondary manifestation of the disease.

ICD-O code: 9719/3

Synonyms
REAL: angiocentric T-cell lymphoma; EORTC used to include in CTCL, large cell, CD30- and CTCL, pleomorphic, small/medium-sized

Epidemiology
Extranodal NK/T-cell lymphoma is a rare disease occurring in adults, with a male predominance. This lymphoma is more prevalent in Asia, Central America and South America.

Etiology
It is universally associated with EBV, and genetic factors play a role in susceptibility to the disease (443,1689).

Localization
The majority of patients present with skin lesions affecting more than one anatomic region, most commonly the trunk and extremities (443,1660).

Clinical features
Cutaneous involvement consists of tumour nodules and plaques. Systemic symptoms such as fever, malaise and weight loss are common. Some cases are accompanied by a haemophagocytic syndrome. The disease is closely related to aggressive NK-cell leukaemia, which also may have cutaneous manifestations, and is also EBV-associated.

Histopathology
A dense dermal infiltrate is often centred on the skin appendages and blood vessels resulting in a column-like low power appearance (1689). Prominent angiocentricity and angiodestruction are often accompanied by extensive necrosis (443,1689). Extension into the subcutis is common. Approximately 30% of cases show at least focal epidermotropism (1689). The mitotic rate is high and apoptotic bodies are numerous. NK/T-cell lymphoma has a broad cytologic spectrum ranging from small to large cells, with most cases consisting of medium sized cells. The cells often exhibit irregular nuclear foldings, moderately dense chromatin, and pale cytoplasm.

Immunoprofile
The most common immunophenotype is: CD2+, CD56+, surface CD3-, cytoplasmic CD3+ε+, CD43+ and cytotoxic granules + (TIA-1, granzyme B, perforin) (1325). Occasional cases are CD56-, but then require EBV positivity or presence of cytotoxic granules for diagnosis; otherwise they should be classified as peripheral T-cell lymphoma, unspecified. LMP-1 is inconsistently expressed, with EBER in situ hybridization preferred for diagnosis.

Genetics
The T-cell receptor is usually in germline configuration.

Prognosis and predictive factors
Extranodal NK/T-cell lymphoma presenting in the skin is a highly aggressive tumour with a median survival of less than 15 months (443,1660). The most
important factor predicting poor outcome is the presence of extracutaneous involvement at presentation (1660). Preliminary data indicate that co-expression of CD56 and CD30 may be associated with a better prognosis (1660, 1690).

**Hydroa vacciniforme-like cutaneous T-cell lymphoma**

**Definition**
Hydroa-vacciniforme-like cutaneous T-cell lymphoma is a rare EBV-associated lymphoma of cytotoxic T-cell or NK-cell origin that affects children, characterized by a vesiculopapular skin eruption that clinically resembles hydroa vacciniforme.

**Synonym**
Angiocentric cutaneous T-cell lymphoma of childhood

**Epidemiology**
Hydroa vacciniforme-like CTCL affects children and teenagers, with almost all reported cases being from Latin America (such as Peru, Bolivia, Mexico) (166, 1479, 1991) and Asia (such as Korea and Japan). Boys and girls are affected in an equal ratio (471, 765).

**Etiology**
The strong association with EBV suggests a pathogenetic role of the virus and genetic predisposition, as in extranodal NK/T-cell lymphoma. The anatomic distribution of the skin lesions suggests sun exposure as a risk factor although tests for minimal erythema doses are usually within normal limits.

**Localization**
The lesions occur predominantly in sun-exposed areas, particularly the face and limbs.

**Clinical features**
Patients present with facial and hand oedema and a papulovesicular eruption that affects sun-exposed and to a lesser extent sun-protected areas. Individual lesions start with oedema and erythema and then progress to vesicles, necrosis, ulceration, crusts, and heal as varicelliform scars. Fever, wasting, hepatosplenomegaly, lymphadenopathy and hypersensitivity to insect bites are common. Some cases are accompanied by a haemophagocytic syndrome. The disease may progress to lymph node and visceral involvement.

**Histopathology**
The infiltrate consists of medium-sized atypical lymphoid cells set in an inflammatory background. The depth of the infiltrate seems related to the age of the lesion (166). A fully developed lesion shows a dense dermal infiltrate with epidermotropism and extension into the fat in a lobular fashion. Ulceration is common. The infiltrate is often angiotropic/angioinvasive and in addition may display a periadnexal and perineural growth pattern.

**Immunoprofile**
The tumour cells are cytotoxic T-cells, that have often lost expression of some pan T-cell markers. The most common phenotype is: CD2+, CD3+, CD8+, CD43+, CD45RO+, TIA-1+, Granzyme B++; CD4-, CD5-, CD7-. CD56 is variably positive, but CD57 is negative. CD30 reactivity can be seen in a subset of cells (<30%).

**Somatic genetics**
The T-cell receptor gene is clonally rearranged (166, 1479), although in cases of NK-cell derivation, T-cell receptor genes are germline.

**Prognosis**
The prognosis is poor, with a 2-year survival rate of 36% (166).
Cutaneous involvement in primary extracutaneous T-cell lymphoma

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Systemic peripheral T-cell lymphoma (PTL), unspecified, involves the skin in approximately 20-30% of the cases (836, 1453). Skin lesions may be present at diagnosis or can develop during disease progression. Lesions are most often tumours or nodules that may be solitary or multiple. No sites of predilection have been recorded. The histological and phenotypic features are identical to the systemic disease. The prognosis is very poor (104,690,836,1453).

**Systemic anaplastic large cell lymphoma (ALCL)**

Primary systemic anaplastic large cell lymphoma affects lymph nodes and extranodal sites, including in 20% of the cases the skin. The skin lesions may be present at diagnosis or can develop at relapse or during disease progression. The skin lesions are usually tumours or nodules that can be solitary or multiple. No sites of predilection have been recorded. The histological, phenotypic and genotypic features are identical in lymph nodes and the skin. The tumour cells are most often large with abundant cytoplasm and characteristic so-called hallmark cells with eccentric, horseshoe- or kidney-shaped nuclei often with an eosinophilic region near the nucleus. The principal morphological variants are the small cell variant and the histioyte rich variant (809). It is important to distinguish these lesions from primary cutaneous ALCL. The histological appearance of systemic cases is usually more monomorphic with infrequent tumour giant cells. The tumour cells in systemic ALCL express a cytotoxic phenotype and are positive for CD30 and EMA. CD3 is negative in more than 75% of cases (191, 1121). CD5 and CD7 are often negative. CD2, CD4 and CD43 are more useful and are expressed in a significant proportion of cases. ALK expression and t(2;5) or variant translocations involving ALK and fusion partners other than NPM are present in the majority of cases (706, 809). The natural history is aggressive but long term complete remissions can be obtained in most patients with ALK-positive disease (191).

**Angioimmunoblastic T-cell lymphoma (AITL)**

Skin lesions in angioimmunoblastic T-cell lymphoma (AITL) occur in half of the cases, usually as a generalized maculopapular eruption simulating viral exanthem or drug eruption, or as urticaria, purpura, erythematous plaques, prurigo-like lesions, erythema-squamous plaques, prurigo-like lesions, erythema-squamous plaques, prurigo-like lesions, erythema-squamous plaques, or necrotic lesions. The disease occurs mostly in middle-aged or elderly people without gender preponderance (787). Other findings are fever, weight loss, night sweats, lymphadenopathy, hepatosplenomegaly, anaemia, an elevated sedimentation rate, leukocytosis, neutropenia or thrombocytopenia, as well as polyclonal hypergammaglobulinemia. AITL exhibits an aggressive course with a median survival ranging from 11 to 30 months and a fatal outcome in 50 to 70% of patients. Histologically, the skin lesions are characterized by nonspecific subtle superficial perivascular infiltrates composed of eosinophils and lymphocytes without atypia accompanied by hyperplasia of capillaries. Admixed plasma cells and histiocytes can be found (2087). Clonal T cell receptor rearrangement has been reported in some cases (1522). However, it is not clear whether the cutaneous manifestations are generally due to tumour cell involvement or a secondary phenomenon related to cytokine production.

Fig. 4.45 Cutaneous involvement in AITL. A polymorphous perivascular infiltrate is present in the superficial dermis.
**Cutaneous marginal zone B-cell lymphoma**

**Definition**
Primary cutaneous marginal zone B-cell lymphoma (MZL) is an indolent lymphoma composed of small B cells including marginal zone (centrocyte-like) or monocytoid cells, lymphoplasmacytoid cells and plasma cells. It is considered part of the broad group of extranodal marginal zone B-cell lymphomas commonly involving mucosal sites (mucosa associated lymphoid tissue, MALT). Primary cutaneous immunocytoma, primary cutaneous plasmacytoma and cutaneous follicular lymphoid hyperplasia with monotypic plasma cells are considered variants of MZL.

**ICD-O code** 9699/3

**Synonyms**
EORTC (1997): Primary cutaneous immunocytoma / marginal zone B-cell lymphoma

**Epidemiology**
MZL most commonly affects adults aged over 40 years. There is no clear gender preponderance (132,2141).

**Etiology**
In Europe, Borrelia burgdorferi DNA has been identified in some cases of MZL suggesting that it may play an etiological role (433). However, no association of Borrelia with CBCL has been found in the United States and Asia (2547).

**Localization**
MZL is predominantly localized on the upper extremities, and less often head and trunk.

**Clinical features**
In most cases, cutaneous MZL presents with red to violaceous plaques or nodules with an erythematous border (2141). Ulceration and visceral dissemination are uncommon. MZL with secondary spread to the skin is often multifocal (1418).

**Histopathology**
The infiltrate is characterized by residual reactive lymphoid follicles surrounded by pale staining cuffs of tumour cells. Reactive germinal centres with distinct mantle zones are commonly found in early lesions but may become colonized by tumour cells as the disease progresses. The interfollicular infiltrate is composed of small to medium-sized, centrocyte-like or monocytoid cells with slightly irregular nuclei, moderately dispersed chromatin, inconspicuous nucleoli and a rim of pale cytoplasm (2234,2362). Variable numbers of lymphoplasmacytoid cells and plasma cells are typically present at the periphery of the infiltrates or in the subepidermal area. Intranuclear PAS positive pseudoinclusions (Dutch burd bodies), are commonly found, particularly in plasma cell rich forms of MZL. Diffuse infiltrates almost completely consisting of monocytoid cells, lymphoepithelial lesions with infiltration of sweat glands and the presence of very immature plasma cells should raise suspicion of secondary cutaneous involvement.

**Immunoprofile**
The neoplastic cells express CD19+, CD20+, CD22+, CD79a+, but are negative for CD5-, CD10-, bcl-6, CD23-, CD43 may be positive (132). In contrast to FL, the tumour cells are bcl-2+, but negative for bcl-6 and CD10 (603,1418). Reactive...
germinal centres are bcl-6+ and bcl-2-.
Anti-CD21 staining often reveals regular
and irregular networks of follicular den-
dritic cells (FDC) in reactive follicles, but
not associated with tumour cells. The
lymphoplasmacytoid cells and the plas-
ma cells show monotypic expression of
immunoglobulin light chains. There are
numerous admixed reactive T-cells.

**Precursor lesion**
Cutaneous lymphoid hyperplasia due to
Borrelia infection may mimic MZL and
has been postulated to represent a pre-
cursor lesion in some circumstances.

**Histogenesis**
Post germinal centre B-lymphocyte with
plasmacytic differentiation and gene
expression pattern (2273).

**Somatic genetics**
IgH genes are clonally rearranged. The
most common translocation in gastric
MZL, the t(11;18) involving the API2/MLT
genes, has not been demonstrated in pri-
mary cutaneous MZL (1418,2141,2279).
However, the t(14;18)(q32;q21) involving
IGH and MALT1 was reported in approx-
imately one third of cases in a small
series. Fas gene mutations are present in
a minority of cases, similar to MZL of
other extranodal sites. Abnormalities of
BCL10 are absent (906).

**Prognosis**
MZL shows a protracted clinical course
with a tendency for recurrences.
However, the prognosis is favourable
with 5-year-survival rates between 90
and 100%. Transformation into diffuse
large B cell lymphoma occurs infrequent-
ly (2141).

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**Fig. 4.49** Plasmacytoid cells in cutaneous marginal zone B-cell lymphoma. 
A Monoclonal plasma cells are admixed with cells with monocytoid features.
B In a sub-
sequent biopsy from the same patient, all of the cells have a plasmacytic morphology and express monoclonal Ig light chains. 
C Kappa. 
D Lambda.
Haematolymphoid tumours

Cutaneous follicle centre lymphoma

Definition
Primary cutaneous follicle centre lymphoma (PCFCL) is defined as a tumour of neoplastic follicle centre cells (FCC), usually a mixture of small and large cleaved cells (centrocytes) and, to a lesser extent, large noncleaved cells (centroblasts) with prominent nucleoli. The growth pattern varies from follicular to follicular and diffuse to diffuse.

ICD-O Code 9690/3

Synonyms
Kiel: centroblastic-centrocytic (follicular, follicular and diffuse), centroblastic.
Working formulation: follicular, follicular and diffuse (predominantly small cleaved, mixed small cleaved and large cell, predominantly large cell).
Reticulohistiocytoma of the dorsum (Crosti disease): \{220\}.

Epidemiology
Primary cutaneous B cell lymphoma (CBCL) in Europe account for up to 25% of cutaneous lymphomas, manifesting predominantly in middle aged adults, with no gender predominance (2523), and having an incidence rate of 0.1-0.2 per 100,000 persons per year (1831). Among primary CBCL, marginal zone B cell lymphoma and FCL are by far the most common subtypes (744,1281,2576).

Etiology
The etiology of primary cutaneous FCL is unknown.

Localization
Most patients have local or regional disease. Trunk and head and neck regions are by far the most frequent localizations \{429,744,2061,2523\}. Presentation with multifocal skin lesions is observed in a small minority of patients.

Clinical features
The clinical presentation consists of firm erythematous to violaceous plaques, nodules or tumours of variable size. Larger nodules may be surrounded by small papules and slightly infiltrated, sometimes figurate plaques. The skin surface is smooth. Lesions may be present for months to many years \{220, 2061,2523\}.

Histopathology
The infiltrates show a spectrum of growth patterns, with a morphologic continuum from follicular to follicular and diffuse to diffuse. The lesions are by definition composed of a mixture of centrocytes (which may be small and/or large) and centroblasts in varying proportion. Small centrocytes and a predominantly follicular growth pattern are more frequently found in small, early lesions. A predominance of large neoplastic cells, particularly large centrocytes or multinucleated cells and less frequently centroblasts (not in confluent sheets), are generally found in more advanced lesions (large nodules or tumours) \{2523\}. When morphologically identifiable, follicles are often ill-defined and show a monotonous population of FCC, lack starry sky histiocytes, and generally have an attenuated or absent mantle zone, different from cutaneous follicular hyperplasias \{425, 429,603,864,1397\}. The infiltrates are found primarily in the dermis, with extension into subcutaneous tissue seen in larger nodules. The overlying epidermis is generally unaffected.

Immunoprofile
The cells express B-cell markers including CD19, CD20, and CD22, and may show (more often in cryostat sections)
monotypic staining for surface immunoglobulins (sIg). However, absence of detectable sIg staining is common in tumours showing a diffuse population of large FCC. In PCFCL, neoplastic cells consistently express Bcl-6 protein, while CD10 is variably expressed (often positive in follicular cases and more frequently negative in lesions with diffuse pattern of growth) \{425, 429, 823, 1042, 1832, 2061\}. Bcl-2 protein is usually not expressed but may be faintly positive, less than reactive T-cells \{38, 209, 425, 603, 774, 1042, 1622\}. The follicles are associated with follicular dendritic cells, positive for CD21, CD23, and CD35. Residual, scattered FDC may be sometimes found in diffuse large cell infiltrates. Neoplastic cells are constantly CD5- and CD43-negative. Admixed T-cells may be abundant and sometimes predominant, particularly in small, early lesions.

**Histogenesis**

Mature germinal centre derived B-lymphocyte \{2273, 2523\}.

**Somatic genetics**

Clonally rearranged immunoglobulin genes are present. Bcl-2 gene rearrangement and t(14;18) chromosomal translocation are absent in most cases \{209, 430, 467, 1622, 1820, 2523\}. Inactivation of p15 and p16 tumour suppressor genes by promoter hypermethylation has been reported in about 10% and 30% of PCFCL, respectively \{468\}. Chromosomal imbalances have been identified by comparative genomic hybridization (CGH) analysis in a minority of PCFCL, but a consistent pattern has not been emerged \{942, 1503\}.

**Prognosis and predictive factors**

Primary cutaneous FCL have an excellent prognosis (>95% 5-year survival). Local recurrences, most often near the initial site of cutaneous presentation, may develop but will not influence clinical outcome. Cytologic grade or growth pattern (follicular or diffuse) do not appear to have an impact on prognosis in patients with primary cutaneous disease. Locally directed forms of therapy, most commonly radiation or surgical excision (small, isolated lesions), are generally effective \{194, 429, 1283, 1824, 1825, 1938, 2060, 2061, 2202, 2523\}. These secondary cutaneous forms are managed like a systemic lymphoma. Whether cutaneous involvement by FCL has an impact on prognosis is presently unknown.

**Secondary cutaneous follicular lymphoma (FL)**

Patients more often present with multiple lesions in non-contiguous skin sites \{429, 2060\}. Unlike PCFCL, neoplastic cells strongly express CD10 and Bcl2, and show t(14:18) translocation in most cases. These secondary cutaneous forms are managed like a systemic lymphoma.
Cutaneous diffuse large B-cell lymphoma

Definition
Primary cutaneous diffuse large B-cell lymphomas (DLBCLs) are neoplastic proliferations showing a completely diffuse growth pattern consisting of large transformed B-cells without significant admixture of centrocytes. The most common variant, DLBCL, leg-type, usually occurs on the leg and less frequently at other sites. Other variants are referred to as DLBCL, other and comprise T-cell/histiocyte-rich LBCL, plasmablastic lymphoma and lesions that do not fulfill the criteria for a DLBCL, leg type.

ICD-O code 9680/3

Diffuse large B-cell lymphoma (DLBCL), leg-type

Epidemiology
Approximately 5-10% of cutaneous B-cell lymphomas are classified as DLBCL, leg type. The median age is around 70 years, and the tumours are more common in females than males (2432). DLBCL of the skin is rare in children (1005).

Clinical features
DLBCL, leg type occurs primarily in elderly females who present with rapidly developing multiple tumours, most commonly on the leg but sometimes at other localizations. Therefore analogous to the “nasal-type” designation for a distinct extranodal variant of NK/T-cell lymphomas, the term “DLBCL, leg-type” is chosen for all cutaneous diffuse large B-cell lymphomas with the designated cytological and immunophenotypic features. Clinically multiple disseminated or aggregated dome shaped red tumours with a firm consistency and a shiny surface without scaling are seen. Ulceration may occur in advanced stages.

Histopathology
The tumour cells diffusely infiltrate the dermis with a destructive growth pattern, often obliterating adnexal structures. The infiltrate may extend into subcutaneous tissue. The epidermis is often spared, with a Grenz zone. The infiltrate is composed of medium to large sized B cells, which are usually monomorphic in appearance. Cells may resemble immunoblasts, and less commonly centroblasts. There is usually a minimal inflammatory component and little stromal reaction.

Immunohistochemistry
The tumour cells are positive for CD20 and CD79a, negative for CD10 and CD138, have variable BCL-6 expression and are usually strongly positive for BCL-2 protein and MUM-1/IRF-4 (1797). These features have been shown in nodal DLBCL to correlate with an activated B-cell gene expression profile, which is usually predictive of a more aggressive clinical course (1041, 1977).

Histogenesis
Transformed peripheral B cell of probable post germinal centre origin (816).

Somatic genetics
The immunoglobulin genes are clonally rearranged. The BCL-2/JH translocation is absent (814,905,2472). Recent studies using gene expression profiling have identified increased expression of genes associated with cellular proliferation. The gene expression profile of the leg-type of tumour resembles that of activated B-cell type of nodal or systemic DLBCL (1041) Significant differences have not been identified among tumours of the leg-type arising in different sites (814,1797).

The primary cutaneous large B-cell lymphoma of the leg-type can be seen in a variety of anatomic locations and is not restricted to the leg (1797).

Prognosis and Predictive factors
In multivariate analysis, BCL-2 expression, multiple skin lesions, and age remained independent prognostic factors. The 5-year disease-specific survival rates in BCL-2–positive and BCL-2–negative patients were 41% and 89%, respectively (P < .0001). 11,12 13 Thus, these studies support the identification of DLBCL leg type, as a clinically and biologically distinctive group.

Diffuse large B-cell lymphoma, other

Fig. 4.53 Diffuse large B-cell lymphoma. A Dome-shaped nodules and tumours without ulceration on the trunk and in the face. B Soft tumour surrounded by an erythematous infiltrate on the back. C Aggregation of non-ulcerated nodules and tumours confined to a limited area of the lower leg.
Definition
The term DLBCL, other, refers to diffuse lymphomas composed of large transformed B-cells that lack the typical features of DLBCL, leg-type, and do not conform to the definition of primary cutaneous follicle centre lymphoma. These tumours may be comprised of a monomorphic population of centroblast-like cells, but with a mixed inflammatory background. BCL-2 protein may be negative, whereas BCL-6 will usually be expressed. The presence of multiple lesions is a poor prognostic indicator; such cases must be distinguished from secondary involvement by DLBCL.

There are some primary cutaneous follicle centre lymphomas in which the majority of tumour cells are centroblasts. Previously these lesions have been categorized as DLBCL by most observers (864,877,879,1263). These lymphomas invariably contain a population of centrocytes as well as some reactive cells. A focal follicular growth pattern may be seen. Despite the predominance of centroblasts, clinical studies have suggested that these lymphomas have a benign clinical course, and may usually be treated in a conservative manner. Based on the clinical behaviour and the spectrum of cytological composition, these tumours are classified under the single heading of cutaneous follicle centre lymphoma.

T-cell / histiocyte-rich large B-cell lymphoma
T-cell / histiocyte-rich large B-cell lymphoma is an unusual morphological variant of “diffuse” LBCL (1886) that rarely occurs primarily in the skin (645,1423). It is characterized by a small number of large neoplastic B-cells (<10%), scattered within an abundant background of small reactive T-lymphocytes with or without histiocytes. Some T-cell/histiocyte-rich large B-cell lymphomas may represent progression from a more indolent B-cell lymphoma (645,2042).

Plasmablastic lymphoma
Plasmablastic lymphomas rarely may present as a primary cutaneous lymphoma. The tumour cells can be positive for Epstein Barr virus (EBV), and have a phenotype that reflects terminal stages of B-cell differentiation (CD20-, MUM-1+, CD138+, EMA+). Plasmablastic lymphomas are usually a heterogenous group of disease entities (524) and can be encountered in settings of immunodeficiency, HIV-associated, or iatrogenic (617,985).

Secondary skin involvement by diffuse large B-cell lymphoma
Secondary skin involvement most commonly shows localisation of the disease on the trunk and the extremities (1263). The prognosis is worse than in primary DLBCL, which can be controlled by local treatment modalities, particularly if one is dealing with a single lesion.
Intravascular large B-cell lymphoma

**Definition**
Intravascular large B-cell lymphoma (IL) is a rare disease with multiorgan involvement, which also affects the skin. This extranodal subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by the presence of large lymphoid cells within the lumina of small to medium-sized blood vessels, particularly capillaries and postcapillary venules. Skin is a common site of presentation, but most patients have systemic disease at time of diagnosis (696,2523).

**ICD-O code** 9680/3

**Synonyms**
Intravascular lymphomatosis; intravascular lymphoma; angioendotheliomatosis proliferans systematisata; malignant angioendotheliomatosis; angiotropic large cell lymphoma (Lukes-Collins), diffuse large B-cell lymphoma (REAL) intravascular large B-cell lymphoma (WHO).

**Epidemiology**
IL is rare and can occur at any age, but most patients are in their 6th – 9th decade of life. Male to female ratio is 0.8 (range 0.7 – 5.0) (2566).

**Localization**
Dermatological manifestations are present in up to one third of patients. Sites of predilection are the lower extremities, but lesions may involve all parts of the integument. A wide range of organ involvement has been described: central nervous system, skin, adrenal glands, thyroid, gastrointestinal system, kidneys, lungs, genitourinary tract, and eye (275). At autopsy, involvement of the majority of organs is seen despite the absence of prior clinical manifestations or mass lesions (1257).

**Clinical features**
The clinical manifestations are predominantly neurologic (85%) (214) and dermatologic (633) and are attributed to vascular occlusion. There is a notable absence of lymphadenopathy, splenomegaly or circulating lymphoma cells in the majority of cases (631,684, 837, 1257,2387). There is a plethora of different skin lesions including tender, indurated nodules, livedo-like reticulate erythema, linear erythematous streaks, and painful indurated telangiectasias. Lesions may imitate phlebitis, panniculitis, or vasculitis (1809).

**Histopathology**
The angiotropic lymphoid infiltrate often spares the dermis, requiring deep biopsies including parts of the subcutaneous fat. The large neoplastic lymphoid cells are usually confined to the lumina of capillaries and postcapillary venules (1809, 2513), albeit extravascular involvement may occur (1257). Tumour cells are large with vesicular nuclei, prominent nucleoli, and frequent mitoses. Fibrin thrombi in the upper and deep dermal plexus, with partial occlusion of the vascular lumina, and few entrapped hyperchromatic lymphocytes are typical of IL presenting with reticulate and livedoid erythema.

**Immunoprofile**
Tumour cells usually express B-cell associated antigens and may coexpress CD10 or CD5. (406,697,953,1193,1253, 2566). Although most IL present with overexpression of theBCL-2 protein (1257) they lack BCL-2 gene rearrangement (1193,2566). These cases have to be distinguished from other intravascular lymphomas of different lineages (112, 113,633,697,736,1355,2138,2143). The precise mechanisms of lymphoid-endothelial interaction leading to vascular occlusion and thrombotic events are

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**Fig. 4.58** Intravascular large B-cell lymphoma. A Involvement of the cutis with livedoid palpable erythema. B Dilated dermal vessels filled with densely packed neoplastic lymphoid cells.
Intravascular large B-cell lymphoma

not clear. The intravascular trapping of lymphoid tumour cells might be the result of a defect in homing receptors and adhesion molecules on the neoplastic cells and the endothelial cells (737, 1852).

**Histogenesis**
The postulated cell of origin is a post follicle centre transformed peripheral B-cell.
Lymphomatoid granulomatosis

Definition
Lymphomatoid granulomatosis (LYG) is an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of Epstein Barr virus (EBV)-positive B-cells, admixed with numerically predominant T-cells. The skin is the most common extrapulmonary site of involvement.

ICD-0 code 9766/1

Synonyms
Angiocentric immunoproliferative lesion (1432), angiocentric lymphoma.

Epidemiology
LYG is rare, usually presenting in adult life. It affects males more often than females (at least 2:1) (1223).

Etiology
Patients with underlying congenital or acquired immunodeficiency are at increased risk for LYG (921,949). Predisposing conditions include allogeneic organ transplantation, Wiskott-Aldrich syndrome, human immunodeficiency virus infection, and X-linked lymphoproliferative syndrome.

In patients without evidence of underlying immunodeficiency, reduced immune function can usually be demonstrated upon careful clinical or laboratory analysis (2534).

Localization
Skin is the most common site of involvement outside the lung (25-50%), but cutaneous involvement is rarely seen without pulmonary disease. Extremities and trunk are the most frequent localizations (185,393,1047,1124,1223,1560).

Clinical features
Patients usually present with signs and symptoms related to the respiratory tract (1124,1223,1426). Skin lesions consist of multiple erythematous dermal papules and/or subcutaneous nodules (185). Necrosis and ulceration are generally associated with larger nodules. Indurated plaques, lichen sclerosus et atrophicus-like lesions, and alopecia are less commonly seen (185,1129). Cutaneous lesions rarely precede pulmonary disease, and are seen either at diagnosis (30%) or later in the course (185). Other sites of involvement include brain (26%), kidney (32%), liver (29%) (1124). Lymph nodes and spleen are spared.

Histopathology
LYG is characterized by an angiocentric and angiodestructive lymphohistiocytic infiltrate. Most cutaneous lesions show infiltration of subcutaneous fat, with or without dermal involvement. Lymphocytic vasculitis is frequent, and fibrinoid necrosis may be present (2339). Well-formed granulomas are usually absent, but a granulomatous reaction may be seen secondary to fat necrosis.

Immunohistochemistry
While EBV-positive B-cells are readily found in the lung, they are generally rare in skin, with the predominant cell being a CD3+, CD4+ lymphocyte (185).

Histogenesis
Mature B lymphocyte, transformed by EBV.

Somatic genetics
The ability to detect clonal immunoglob-
ulin heavy chain gene rearrangement is related to grade, with clonal B-cell populations usually found only in grade 2-3 lesions. Southern blot, polymerase chain reaction (PCR), and in situ hybridization techniques can be used to detect EBV sequences (921,1224,1560).

**Prognosis and predictive factors**
The natural history of LYG is variable (714,1223). In some patients it may follow a waxing and waning clinical course, with spontaneous remissions without therapy. However, in most patients the disease is more aggressive, with a median survival of less than two years. Histological grade and clinical aggressiveness relate to the proportion of EBV+ B-cells, but even grade 3 lesions may show spontaneous regression (2534). The most common cause of death is progressive pulmonary involvement. Skin lesions may appear, without evidence of relapse at other sites (185,2534).
Mantle cell lymphoma

Definition
Mantle cell lymphoma is a B-cell lymphoma that almost always overexpresses cyclin D1 and is composed either of small lymphocytes bearing some resemblance to centrocytes or, in the blastoid variant, by cells resembling lymphoblasts or large B-cells. Neither classic centroblasts nor paraimmunoblasts are present.

ICD-O code 9673/3

Epidemiology
MCL occurs in middle aged to older individuals with a male predominance and accounts for up to 10% of all non-Hodgkin lymphomas (2301).

Clinical features
Most patients present with adenopathy and stage III/IV disease. Hepatosplenomegaly and bone marrow involvement are common and peripheral blood involvement is seen in about 25% of patients. Gastrointestinal disease is also common but often subtle (2254).

Cutaneous MCL
Skin involvement is rare (2-6% of cases) (2030) but when it occurs, is usually, but not always, seen at initial presentation and associated with extracutaneous disease (654,2132). Rare cases that appear to be primary are described. Lesions are most common on the thorax and extremities and usually occur as multiple erythematous macules, papules, plaques or nodules (654,2132).

Histopathology
MCL are usually composed of relatively small lymphocytes with slightly irregular to very clefted nuclei and somewhat dispersed chromatin. In the blastoid variant, which may be relatively more common in cutaneous lesions, the cells either have very dispersed chromatin with inconspicuous nucleoli resembling lymphoblasts, or are larger and more pleomorphic, sometimes with very prominent nucleoli, resembling cells of a diffuse large B-cell lymphoma.

MCL infiltrates in the skin occur in the dermis sometimes with extension to the subcutaneous tissue. A grenz-zone should be present. The infiltrate may be relatively scanty and perivascular/periappendageal, form nodules or be very dense and diffuse. A mantle zone growth pattern with MCL growing around reactive germinal centres may occur (219,654). Admixed inflammatory cells may be present (654).

Immunohistochemistry
MCL are distinguished in most cases from other non-Hodgkin lymphomas by their frequent but not invariable CD5+, CD10-, CD23-, cyclin D1+, BCL-6-, CD20+ light chain class restricted phenotype (376,2301,2303). Cyclin D1 staining can be problematic and CD5 not always positive. With one interesting exception, the cases are negative for the cutaneous lymphocyte-associated antigen (2132).

Histogenesis
Mature B-cell, probably of the inner mantle zone, usually but not always with unmutated immunoglobulin heavy chain genes.

Somatic genetics
Immunoglobulin genes show clonal rearrangement in all cases and in many, but not all, cases they lack somatic hypermutation (1756,2451). The vast majority of MCL have a t(11;14)(q13;q32) translocation involving the CCND1 (cyclin D1) and immunoglobulin heavy chain genes with subsequent CCND1/ cyclin D1 overexpression (376, 2303). The most sensitive technique to document the translocation in diagnostic specimens is cytogenetic fluorescence in situ hybridization (FISH) analysis.

Fig. 4.63 Mantle cell lymphoma. A Nodular perivascular and periappendageal infiltrates in all layers of the dermis. A subepidermal grenz-zone is present. B Tumour cells show nuclear immunoreactivity for cyclin D1.
Gene profiling has suggested the presence of a small subset of cases that lack cyclin D1 abnormalities (1978). Other primary and mostly secondary abnormalities are also described (376,1045,2303).

**Prognosis and predictive factors**

MCL has a median survival of 3-5 years with those having “non-nodal” disease doing better (376,1756,2301,2303). Adverse prognostic indicators include a high proliferative fraction, probably blastoid morphology, secondary genotypic abnormalities and blood involvement (at least in patients with nodal disease). Whether skin involvement in particular is an independent prognostic indicator is uncertain.

**Burkitt lymphoma**

**Definition**

Burkitt lymphoma is a mature B-cell neoplasm composed of relatively uniform medium sized transformed B-cells with a C-MYC translocation (630).

**ICD-O code** 9687/3

**Epidemiology**

BL occurs in children in equatorial Africa (endemic), primarily in children and young adults elsewhere (sporadic) and in immunodeficient patients. There is a male predominance.

**Etiology**

Endemic BL and a minority of sporadic BL are Epstein-Barr virus positive.

**Clinical features**

BL usually presents as an extranodal mass often in the abdomen or, in endemic cases, in jaw or other facial bones. Other patients have a leukaemic presentation. Cutaneous involvement in BL appears to be extremely rare and at least usually is associated with disease at other sites (123,141,349,700). It has rarely been described as occurring with ulceration from direct invasion from underlying bony lesions (349), as distinct cutaneous lesions at relapse (123) and in 12% of autopsied cases of American BL (2 cases) (141).

**Histopathology**

Histologic sections show a diffuse proliferation of medium sized transformed lymphocytes with relatively round nuclei with several nucleoli and a narrow rim of very amphophilic/basophilic cytoplasm. There are many apoptotic bodies and tingible body macrophages creating a starry sky appearance. Skin involvement demonstrates a diffuse but sometimes patchy dermal and subcutaneous infiltrate with a Grenz zone (123,700).

**Immunohistochemistry**

Immunophenotypic studies demonstrate CD5-, CD10+, BCL-2-, CD20+ mature B-cells with surface immunoglobulin expression.

**Histogenesis**

Germinal centre/post germinal centre B-cell

**Somatic genetics**

All cases have clonal immunoglobulin gene rearrangements and a C-MYC translocation, most often with a t(8;14)(q24;q32) (1483). Many, if not all, cases also have C-MYC mutations (230, 1483).

**Prognosis and predictive factors**

BL is an aggressive but curable neoplasm with a 5 year overall survival of 44% (3).

**Chronic lymphocytic leukaemia / small lymphocytic lymphoma**

**Definition**

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell neoplasm composed of small, usually CD5+, CD23+, cyclin D1- B-cells with relatively round nuclei having clumped chromatin (1662). Especially in lymph nodes, there is often an associated minor population of prolymphocytes and paraimmunoblasts that form proliferation centres.

**ICD-O code**

<table>
<thead>
<tr>
<th>Chronic lymphocytic leukaemia</th>
<th>9823/3</th>
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<tr>
<td>Small lymphocytic lymphoma</td>
<td>9670/3</td>
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</table>

**Epidemiology**

CLL is the most common type of leukaemia in the West and SLL are reported to account for 6.7% of non-Hodgkin lymphomas (3,1064).
Clinical features
CLL/SLL is seen most commonly in middle aged and older adults with a male predominance. It usually presents with blood and marrow involvement, frequent adenopathy and sometimes hepatosplenomegaly. Skin involvement is reported in 2% of patients without a marked predilection for any region of the body and occurs in patients who also have blood involvement (273,1167). The face and scalp are frequent sites of involvement. It may be present either at the time of diagnosis or, much more frequently, develops subsequently (431). Lesions may be single or multiple erythematous macules, papules, violaceous plaques, nodules or tumours either occurring in a limited or less frequently more generalized area (431,1167). Atypical presentations include chronic paronychia, papulovesicular eruption and finger clubbing. Skin involvement may occur at sites of previous viral (eg, herpes zoster, herpes simplex) or Borrelia burgdorferi infection (427) and at sites of epithelial neoplasms (2215). Spontaneous regression of CLL infiltrates at least at sites of prior herpetic infection may occur (2449). In contrast to the absence of virus in at least most of the lesions in viral scars, B. burgdorferi DNA is found in at least some cutaneous CLL lesions (427).

Histopathology
Histologic sections demonstrate a diffuse proliferation of small relatively round lymphocytes with condensed chromatin with lymph node biopsies typically demonstrating paler (pseudofollicular) proliferation centres where the cells have more abundant pale cytoplasm, more dispersed chromatin and sometimes prominent central nucleoli. The latter cells represent paraimmunoblasts and some of the former cells prolymphocytes. Cutaneous lesions show a patchy perivascular, nodular, more diffuse or rarely band-like dermal infiltrate of small, usually but not always round, lymphocytes with occasional single lymphocytes in the epidermis and frequent extension into the subcutaneous tissue (431). Patients with more than one biopsy can demonstrate more than one growth pattern. There may be overlying epidermal changes infrequently including ulceration. Proliferation centres are seen only in a minority of cases although there may be scattered larger cells in other cases (427). A minority of cases have admixed eosinophils, neutrophils, and/or histiocytes. A granulomatous reaction may be present especially in some of the lesions arising in scars following prior viral infection (432). Cutaneous CLL associated with granuloma annulare-like changes has also been reported (797).

Immunoprofile
Immunophenotypic studies demonstrate a characteristic CD5+, CD43+, CD10-, CD23+, FMC7-, cyclin D1-, weakly CD20+ monoclonal B-cell population with weak surface immunoglobulin expression (1662). In the cutaneous lesions, the admixed T-cells present are mostly of CD4+ type (431).

Histogenesis
Mature B-cell most likely of memory type (including cases with either mutated or unmutated immunoglobulin heavy chain genes) (586,1288,1976).

Somatic genetics
All cases have clonal immunoglobulin gene rearrangement although oligoclonal bands suggesting admixed reactive B-cells may also be present in the cutaneous lesions (431). In some cases the immunoglobulin genes show somatic hypermutation and in others they do not (586,943,1288,1976). There are no chromosomal abnormalities specific for CLL/SLL; however, the most commonly described abnormalities include 13q and 11q deletions, trisomy 12 and 17q deletion (643).

Genetic susceptibility
There is an inherited susceptibility to CLL; however, the critical genes remain to be determined (1064).

Prognosis and predictive factors
CLL/SLL is one of the indolent lymphoid neoplasms. Clinically advanced stage, 17q deletions, unmutated immunoglobulin genes, CD38 and ZAP-70 expression include some of the more important adverse prognostic indicators (553,643,943,1662,1760,2518). Most do not believe that skin involvement portends an adverse outcome; however, it has been reported that cases with >5% medium and large-sized B-cells, admixed reactive cells and epidermal changes did worse than those without these features and there are reports in the literature suggesting a poor outcome following any cutaneous involvement (427,432,1167). Transformation to a large cell lymphoma (Richter syndrome), Hodgkin lymphoma or prolymphocytic leukaemia is also associated with an aggressive course (826). Richter syndrome can present as cutaneous lesions (427,2578).
Hodgkin lymphoma

Definition
Hodgkin lymphoma (HL) is a neoplasm characterized by large tumour cells of B-cell lineage in a characteristic inflammatory background. It encompasses two entities distinguishable by their morphology and phenotype, namely nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). Cutaneous involvement by NLPHL has not been reported, and is rare in cHL. For details see the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (1121).

ICD-O code
Nodular lymphocyte predominant Hodgkin lymphoma 9659/3
Classical Hodgkin lymphoma 9650/3

Synonym
Hodgkin disease

Epidemiology
Cutaneous involvement by cHL is rare and is seen in <5% of cases, and <1% of cases at presentation (1076,1457, 2326,2505). The incidence appears slightly increased in patients infected with the human immunodeficiency virus (HIV) (2094,2157). cHL has also been reported to occur with increased frequency in patients with mycosis fungoides and cutaneous CD30+ T-cell lymphoproliferative disease (CD30+ LPD), but is usually nodal in localization without cutaneous spread (1123,1176,1324, 2190).

Etiology
The etiology of cHL is not established. However, an association with the Epstein Barr virus has been suggested, especially in cutaneous cases (1340).

Localization and Clinical features
Three mechanisms of cutaneous involvement have been implicated: 1) retrograde lymphatic spread from regional lymph nodes; 2) direct extension, usually from a mass lesion; and 3) haematogenous dissemination (2326,2505). The distribution of cHL lesions relates to the manner of spread. Direct extension is most common in patients with massive mediastinal disease, with involvement of the skin of the chest wall. The lesions are manifested as erythematous papules or nodules. Rare cases of HL presenting as primary disease in the skin have been reported 12 (2195).

Histopathology, immunoprofile and genotype
The histological features resemble those of cHL in other sites. Classical Reed-Sternberg (RS) cells and variants are seen in an inflammatory background. The immunophenotype also is characteristic of cHL, with the neoplastic cells expressing CD30 and CD15 (426,1340). However, while most cases of cHL are of B-cell lineage (1340), cases of cHL with cutaneous involvement may express a T-cell phenotype (595,1176,2527). Such cases are usually associated with concomitant CD30+ LPD. Common clonal T-cell gene rearrangement has been identified in the atypical cells of CD30+ LPD and cHL involving lymph nodes. Because RS-like cells may be seen in CD30+ LPD, the differential diagnosis between these disorders is often difficult.

Prognostic factors
In patients with cutaneous involvement secondary to haematogenous spread, the prognosis is poor. However, other patterns of cutaneous involvement are not necessarily associated with a poor prognosis (415,1023,1457,1651,1987, 2326,2505).

Fig. 4.65 Hodgkin lymphoma. A Secondary involvement of the skin often occurs by direct extension, as in this large cutaneous nodule with ulceration. B cHL, skin. Classical Reed Sternberg cells are present in a background of reactive lymphocytes.
Blastic NK-cell lymphoma

Definition
Blastic NK-cell lymphoma is a clinically aggressive lymphoma, with a high incidence of cutaneous involvement and risk of leukaemic dissemination. The blastic appearance and CD56 expression initially suggested an NK-precursor origin (632). More recent studies suggest derivation from a dendritic cell precursor, as reflected in the designation CD4+, CD56+ haematodermic neoplasm.

ICD-O code 9727/3

Synonyms
CD4+, CD56+ agranular haematodermic neoplasm, blastoid NK-cell lymphoma, monomorphic NK-cell lymphoma

Epidemiology
Blastic NK-cell lymphoma is a rare lymphoma. Currently, there are no reports showing any racial or ethnic predilection. Most patients are middle-aged or elderly (632,1817). However, every age can be affected.

Localization
Blastic NK-cell lymphoma has a predilection for skin. At presentation there may be a single tumour, nodule or plaque (632,1817). Lymph node, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Central nervous system involvement can develop during the course of the disease.

Clinical features
Blastic NK-cell lymphoma frequently involves the skin at presentation with a single tumour, or tumours and plaques. Additionally, lymph nodes, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Most cases of blastic NK-cell lymphoma presenting in the skin progress quickly to develop lymph node, bone marrow, and central nervous system involvement (450,739). The clinical course is aggressive. There may be initial responses to multiagent chemotherapy, but a high risk of relapse. Regimens for both aggressive lymphomas and acute myeloid or lymphoid leukaemias have been utilized.

Histopathology
The dermis contains a dense, monotonous infiltrate of medium-sized cells with finely clumped chromatin, and absent or indistinct nucleoli resembling lymphoblasts or myeloblasts (632,1121, 1817). The cells have sparse cytoplasm. Mitotic figures are frequent. The overlying epidermis is spared, with a distinct grenz zone. Inflammatory cells are absent. There is generally no necrosis or angioinvasion.

Immunoprofile
The tumour cells usually express CD4, CD56, and CD43. Expression of CD7, CD2 is variable, whereas surface and cytoplasmic CD3 are negative (632,1817,2391). Cytotoxic molecules are generally absent. In some cases TdT and/or CD34 can be positive (313,1681,2159). CD68 can be weakly positive, showing focal staining in the Golgi region. Since lymphoblastic and myeloblastic neoplasms can also be positive for CD56, stains for myeloperoxidase, and CD3 should always be performed in order to exclude these entities (2118,2299). The cells express CD123 and TCL1, both of which support a relationship to dendritic cells (450,1012). Blastic malignancies of precursor NK-
Blastic NK-cell lymphoma
cell origin also exist, and may be difficult to distinguish in the absence of specialized techniques (1012,1681,2302). There has been one report showing expression of KIR receptors (1293).

Histogenesis
Based on the expression of CD56, an NK-cell derivation was initially proposed. However, the tumour was considered to be of uncertain lineage in the WHO classification. Recently studies have suggested a derivation from plasmacytoid dendritic cells based on gene expression studies and cytokine production. The cells express high levels of interleukin-3 receptor alpha chain (IL-3R-alpha).

Genetics
T-cell receptor genes are in germline configuration. Tumour cells are negative for EBV.

Prognosis and predictive factors
Blastic NK-cell lymphoma is an aggressive disease with a poor prognosis (311,739). While close to 80% of patients obtained an initial complete remission, the majority of patients relapsed within two years. Patients with single isolated skin lesions appear to have a better prognosis (525).

Fig. 4.67 Blastic CD4+ CD56+. NK-cell lymphoma. Brownish haemorrhagic plaques and infiltrates. From D.V. Kazakov et al (1236).

Fig. 4.68 Blastic CD4+ CD56+. NK-cell lymphoma. Diffuse infiltration of the trunk and upper extremities.

Fig. 4.69 Blastic CD4+ CD56+ NK-cell lymphoma. A Tumour cells diffusely infiltrate the dermis, but not epidermis. Note the finely distibuted chromatin and inconspicuous nucleoli. B Tumour cells are positive for CD4 and C CD56.
Precursor T-lymphoblastic leukaemia/lymphoma and precursor B-lymphoblastic leukaemia / lymphoma

### Definition
Precursor lymphoblastic leukaemia/lymphoma is a malignancy derived from precursor cells of either T-cell or B-cell lineage. There is overlap in the clinical presentation, and patients may present with disease primarily in the bone marrow and peripheral blood (leukaemia) or in solid tissues (lymphoma). Because of similarities in stage of differentiation, and manner of presentation, precursor T-cell and B-cell malignancies will be discussed together.

### ICD-O code
- Precursor T-lymphoblastic leukaemia: 9837/3
- Precursor T-lymphoblastic lymphoma: 9729/3
- Precursor B-lymphoblastic leukaemia: 9836/3
- Precursor B-lymphoblastic lymphoma: 9728/3

### Synonyms
- Acute lymphoblastic leukaemia
- Lymphoblastic lymphoma

### Epidemiology
Lymphoblastic leukaemia/lymphoma is rare. Approximately 3.5% to 7% of all malignant lymphomas of the skin are of the lymphoblastic type (339,2041). Most cases are diagnosed in children and young adults. However, every age can be affected. Precursor B-cell malignancies are more common in skin than those of precursor T-cell origin (470,1431,1489,2043).

### Clinical features
Lymphoblastic lymphoma/leukaemia may initially present in cutaneous or other extranodal sites as a single nodule or tumour (1429,2041). Frequent sites are the head and neck region, especially for patients with precursor B-cell disease (2043). However, there is a high likelihood of occult disease in the bone marrow, and patients should be regarded as having systemic disease for therapeutic purposes.

### Morphology
The dermis contains a monotonous infiltrate composed of small to medium sized cells with fine chromatin and scant cytoplasm, characteristic of lymphoblasts. Nuclear irregularities are variable, and do not correlate with lineage. The epidermis is uninvolved, with a distinct Grenz zone. The cells are interspersed among dermal collagen fibres, without a stromal or inflammatory response.

### Immunoprofile
- **T-cell lymphoblastic leukaemia/lymphoma.** The tumour cells are positive for terminal transferase (TdT), CD43, CD99 (1489,1949,2043). They variably express CD1a, CD2, CD3, CD4, CD5, and CD8. CD10 may be positive in some cases.
- Cytoplasmic CD3 appears before surface CD3. CD7 is nearly always positive (1843). The phenotype reflects stages in the maturation of a thymic T-cell.
- **B-cell lymphoblastic leukaemia/lymphoma.** The tumour cells are positive for TdT, CD43, and CD99 (1489,2043). The cells are usually positive for CD19 and CD79a (326). CD10 is expressed in most cases. CD20, CD22, and CD24 are variably expressed. LCA may be negative. The cells may contain cytoplasmic µ heavy chain, usually in the absence of light chains.

### Histogenesis
Precursor T- or B- lymphoblast.

### Somatic genetics
Rearrangement of immunoglobulin heavy chain genes, and T-cell receptor genes usually correlates with B-cell or T-cell lineage, respectively (544,1311). However, lineage infidelity is common in precursor lymphoid malignancies. Light chain gene rearrangement is a relatively late event in B-cell differentiation. The classification of lymphoblastic malignancies is closely related to a complex series of genetic abnormalities that correlate with pathogenesis and clinical outcome (1121).

### Prognosis and predictive factors
Precursor lymphoblastic leukaemia/lymphoma is an aggressive disease. However, cutaneous involvement is not a poor prognostic factor, and response to systemic multiagent chemotherapy may be excellent (2043).

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**Fig. 4.70** Precursor B lymphoblastic leukaemia/lymphoma. A Soft non-ulcerated tumour on an erythematous plaque without scaling. B Tumour cells expressing CD79a.
Cutaneous involvement by myeloid leukaemia

Definition
Myeloid leukaemia is a heterogenous malignant disorder of myeloid precursor cells characterized by an increase in blast forms in the peripheral blood and bone marrow. Specific skin involvement results from direct infiltration of the skin by neoplastic cells.

Synonyms
Extramedullary myeloid sarcoma, granulocytic sarcoma, chloroma.

Epidemiology
Acute myeloid leukaemia (AML) accounts for 10-15% of childhood leukaemia but the incidence increases steadily with age. More than 50% of patients are older than 60 years (1838). Chronic myelogenous leukaemia (CML) is generally a disease of older adults, with a median age between 50 and 60 years at presentation (1183). Skin involvement is reported to occur in 2% to 30% of patients with AML (35,125,649). Specific skin lesions are equally common among males and females. It is found more frequently in patients with acute myelomonocytic (AMML) and monoblastic/monocytic leukaemias (AMOL). Specific cutaneous lesions are less common in chronic myelomonocytic leukaemia (CMML) and CML.

Clinical features
Specific skin lesions present as solitary or multiple violaceous to red-brown papules, nodules and plaques. The most common sites of involvement are the scalp, face, trunk, and extremities (2288). Haemorrhagic lesions are common. Leukaemic gingival hyperplasia is a striking feature of AMML and AMOL (649). In the majority of cases, specific skin lesions develop in the setting of established leukaemia. In rare instances, leukaemic skin infiltrates may precede peripheral blood and bone marrow involvement (445,589,2368).

Histopathology
There is a moderate or dense, diffuse or nodular infiltrate in the dermis that extends into the subcutaneous fat (329,1172). The epidermis usually is spared. The infiltrates typically show perivascular and periadnexal accentuation. A characteristic feature is the presence of rows of atypical cells between collagen bundles (2137). The infiltrate is composed of medium-sized or large neoplastic cells with round, oval or folded basophilic nuclei. Mitotic figures are usually present. In CML, the infiltrate is more pleomorphic and dominated by mature and immature cells of the granulocytic series. Cutaneous infiltrates of plasmacytoid monocytes may occur in CMML (297).

Immunoprofile
The majority of the tumour cells shows reactivity for lysozyme, myeloperoxidase, CD45, CD43, and CD74. Staining for chloroacetate esterase and CD68 is variable (1172,1899). Staining for CD34 is variable, and often negative in monoblastic leukaemias. The neoplastic cells are negative for CD3, CD20, CD30 and S-100 protein. The presence of CD56 expression in specific skin infiltrates of AML has been reported (1163,1258).

Histogenesis
Haematopoietic stem cells.

Somatic genetics
Genetic studies of specific cutaneous lesions in AML are scant and limited to isolated cases. An increased incidence of trisomy 8 in AML with skin infiltration has been reported (35). Rarely, cases of congenital AML may be present with skin lesions.

Genetic susceptibility
Patients with Down syndrome, Fanconi anaemia, ataxia telangiectasia, Bloom syndrome, and Kostmann syndrome are predisposed to AML.

Prognosis and predictive factors
The prognosis of patients with specific skin lesions of AML is generally poor (125,805). In one series, all patients died within 24 months after onset of skin lesions (1172).
Definition
The term pseudolymphoma (PSL) is defined as a reactive polyclonal benign lymphoproliferative process predominantly composed of either B-cells or T-cells, localized or disseminated. It heals spontaneously after cessation of the causative factor (e.g. drugs) or after non-aggressive treatment.

Synonyms and historical annotation
In 1923, Biberstein coined the term lymphaetosis benigna cutis. Since then, a variety of designations have been proposed: lymphadenosis benigna cutis (124), pseudolymphoma of Spiegler (2237) and Fendt. (721), cutaneous lymphoid hyperplasia and lymphocytoma cutis (401). In retrospect, most of these terms were describing cutaneous B-cell pseudolymphomas (B-PSL). The concept of cutaneous T-cell pseudolymphomas (T-PSL) was not widely accepted until the early 1980's.

Epidemiology
Cutaneous pseudolymphomas affect all age groups with a predilection of Borrelia-induced B-pseudolymphomas in children and young adults, whereas drug induced T-pseudolymphomas more frequently are seen in adults. Even though Borrelia-induced pseudolymphomas may be precursors for B-cell lymphomas of the skin, in general cutaneous pseudolymphomas are selfregressing and do not affect survival.

Etiology
Pseudolymphomatous proliferations in the skin may be induced by microbial, physical or chemical agents including Borrelia burgdoferi infection, tattoos and drugs.

Localization
In most cases, skin lesions are confined to the site of external irritation, i.e. tick bite. Due to the preferential “docking” of ticks to body areas where the skin is relatively soft, e.g., scrotum of young boys, the mamilla, ear lobes, large skin folds are preferentially involved.

Clinical features
Several variants of cutaneous PSL exist, presenting with different clinical symptoms.

Pseudolymphoma (PSL) with predominant T-cell infiltrates (T-PSL)
Lymphocytic infiltration (idiopathic or drug induced)
Palpable migratory arciform erythema
Lymphomatoid contact dermatitis
Actinic reticuloid
Persistent nodular arthropod-bite reactions
Inflammatory molluscum contagiosum

The original description of lymphocytic infiltration (idiopathic or drug induced cutaneous T-cell pseudolymphoma) given by Jessner and Kanof in 1953 (1141) is still valid today. The lesions are flat, discoid, more or less elevated, pinkish to reddish brown, starting as small papules, expanding peripherally, sometimes clearing in the centre, sometimes showing a circinate arrangement. The surface is smooth, occasionally uneven. There is no follicular hyperkeratosis as seen in discoid lupus erythematosus, which may be simulated. There may be only one, a few, or numerous lesions.

Histopathology
Characteristic is a sleeve-like, predominantly lymphocytic infiltrate around the vessels of the upper and mid dermis. In addition, some macrophages and eosinophils may be found. Phenotyping has shown the infiltrate to consist of both B and T cells (423) even though T cells seem to predominate in most cases (2521).

Palpable migratory arciform erythema clinically shows a circinate or annular slightly elevated erythematous lesion.

Table 4.02 Differentiation between B-pseudolymphoma (B-PSL) and cutaneous B-cell lymphoma (CBCL)
Taken from Burg et al. (340).

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<thead>
<tr>
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<th>CBCL</th>
<th>PSL</th>
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<tr>
<td>Clinical features</td>
<td>Number of lesions</td>
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<td></td>
<td>Extracutaneous involvement</td>
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<td></td>
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<tr>
<td></td>
<td>Survival time</td>
<td>affected</td>
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<tr>
<td>Histological features</td>
<td>Pattern of infiltrate</td>
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<tr>
<td></td>
<td>Structure of infiltrate</td>
<td>“infiltrating” between collagen bundles</td>
</tr>
<tr>
<td></td>
<td>Border of the infiltrate</td>
<td>usually absent</td>
</tr>
<tr>
<td></td>
<td>Additional cells</td>
<td>may occur</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Ig heavy chain gene rearrangement</td>
<td>present in most cases</td>
</tr>
</tbody>
</table>

|                | Ig heavy chain gene rearrangement    | present in most cases           | absent in most cases |
|                | Immunoglobulin light chains          | monotypic (kappa or lambda)     | polypotypic expression |
|                | B-cell marker expressing cells       | >50% cells                      | ≤50% cells           |
|                | T-cell marker expressing cells       | usually few                     | >50% cells           |
|                | CD21-positive dendritic cells        | mostly absent                   | mostly present       |
|                | Genotype                            | irregular pattern               | regular pattern      |
Histologically there is a scant sleeve-like perivascular lymphocytic infiltrate in the mid or deep dermis.

Lymphomatoid contact dermatitis has been reported as a reaction to various allergens (i.e. nickel, Peru balsam) or drugs (diphenylhydantoin) inducing mycosis fungoides-like features (1975). Genotyping has shown clonal rearrangement in some cases. Such cases may be closely related to "clonal dermatitis" some of which develop into overt CTCL (2545,2546). Histologically, eczematous features with epidermotropism of lymphocytes and accumulations of CD1a-positive Langerhans cells may be found. Actinic reticuloid is a chronic photoallergic infiltrative dermatitis of light exposed areas associated bearing a clinical and histological resemblance to malignant lymphoma, especially to Sézary syndrome. Histologically there is a dense infiltrate of lymphocytes mixed with many polyclonal plasma cells, eosinophils and macrophages.

There is a considerable overlap between T- and B-PSL in persistent nodular arthropod-bite reaction, nodular scabies and inflammatory molluscum contagiosum which show a dense polymorphous infiltrate consisting of a mixture of T-cells, B-cells, macrophages and predominantly eosinophilic granulocytes.

Lymphomatoid papulosis even though showing biologic features of pseudolymphoma is considered to belong to the group of lymphomas since despite spontaneous regression of single lesions, the disease is not curable and may show transitions to other lymphomas.

**PSL with predominant B-cell infiltrates**

Lymphadenosis benigna cutis (LABC) (124) -the prototype of this group of B-PSL- is synonymous with lymphocytoma cutis. In Europe it is most commonly caused by infection with Borrelia burgdorferi after a tick bite (Ixodes ricinus). However other microbiological (medicinal leeches, Hirudo medicinalis) (2211), physical or chemical agents as well may induce lymphocytoma-like reactions.

Two thirds of all lesions are situated on the head, tending to occur on the ear lobes. Other predilections are the nose, the inguinal area and scrotum. Usually the lesion is a solitary papule or nodule, but several disseminated lesions may occur as well (1068).

Microscopic examination shows a nodular dermal infiltrate with reactive follicles. In addition, there is a rather diffuse infiltrate containing T cells, histiocytes, eosinophils and polyclonal plasma cells. The presence of macrophages containing ingested nuclear material (tingible body macrophages) within the follicles producing a "starry sky" pattern is a common feature in B-PSL and a hallmark of all reactive germinal centres. The infiltrate is predominantly located in the upper and mid dermis, but may extend into the deep dermis. Small groups of lymphoid cells between collagen bundles may be observed at the periphery of the lesions. This is a helpful histological criterion in the differentiation from cutaneous B-cell lymphoma, in which the nodular infiltrate shows convex rather than concave sharply demarcated borders.

Phenotypically (428) a polyclonal B-lymphocytic infiltrate without light chain restriction of the infiltrate is found in most cases. The cells express the phenotype of mature B-cells (CD 20, CD 79a). In B-PSL, regular and sharply demarcated networks of CD21+ follicular dendritic cells are present, whereas in CBCL these networks are irregularly shaped (342).

*Acral pseudolymphomatous angiokeratoma of children (APACHE)* is a rare benign pseudolymphomatous disorder occurring mainly in children (1888). The typical clinical presentation is multiple (up to 40), asymptomatic, small papules located unilaterally on the fingers, toes and hands. Their colour is usually red-violet, accounting for their angiomatous appearance (1887). Histologically the dermis contains a moderately to very dense, non-epidermotropic infiltrate composed of small well-differentiated lymphocytes admixed with a few plasma cells, histiocytes, and giant cells. Blood vessels show prominent plump endothelial cells (1165,1887).

Immunohistochemically the cellular infiltrate represents a mixture of polyclonal mature T- and B-lymphocytes (936).

**Inflammatory pseudotumour (IPT)** (plasma cell granuloma, inflammatory myofibroblastic pseudotumour) refers to a spectrum of idiopathic benign conditions with unknown etiology that can develop in various organs and deep tissues, particularly in the lung. Cutaneous IPT occurs as a solitary, slowly growing, tender nodule measuring 1-3 cm in diameter. Irrespective the anatomic location, the lesions share common histological features, showing well circumscribed proliferation of myofibroblasts/fibroblasts expressing smooth muscle actin (SMA) and vimentin, a mixed cell infiltrate containing high numbers of plasma cells with prominent germinal centres dispersed throughout the lesion. The plasma cells are polyclonal and are seen in the interfollicular areas (plasma cell granuloma) (21, 508,509). Later stages show marked fibrosis/sclerosis with thick collagen bundles arranged in concentric whorls.

**Lymphoid infiltrates of the skin mimicking lymphoma** 213
Histological variations include presence of high endothelial venules, admixture of eosinophils, calcification, psammoma bodies, and presence of large polygonal myofibroblasts (vimentin+, CD15-, CD30-) \(\text{[1476]}\) with single, double or multiple nuclei and prominent eosinophilic nucleoli resembling Reed-Sternberg cells \(\text{(388,1084,1476,1881,2561)}\). Differential diagnosis of cutaneous IPT includes lymphoma, angiolymphoid hyperplasia with eosinophilia and Kimura and infectious dermatoses (mycobacteria, deep fungal infections). The later stages of cutaneous IPT should be distinguished from erythema elevatum diutinum, granuloma faciale and dermatofibroma with lymphoid infiltrate.

**Histogenesis**
Polyclonality is the hallmark of cutaneous pseudolymphomas. Besides T-cells and B-cells, mononuclear phagocytes represent a considerable proportion of the infiltrate. Eosinophils and polytypic plasma cells as well are present in most cases of either B-cell or T-cell pseudolymphomas of the skin \(\text{(342)}\).

**Somatic genetics**
No clonal rearrangement of T-cell receptor genes or of immunoglobulin heavy chain genes or light chain restriction of plasma cells is found.

**Prognosis and predictive factors**
The prognosis of cutaneous pseudolymphomas by definition is excellent, showing spontaneous regression of the lesions after cessation of the causative factor or due to treatment with non-aggressive treatment modalities. However there is a potential for some cutaneous pseudolymphomas to progress to cutaneous B-cell lymphoma (CBCL) \(\text{(433,807,1339)}\), or to cutaneous T-cell lymphoma (CTCL) \(\text{(2545,2546)}\).

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**PSL with mixed and unclassified infiltrates**
There are reactive lymphocytic infiltrates in the context of other skin disorders that can be referred to as pseudolymphomatous reactions in an even broader sense. Neoplasms, especially squamous cell carcinoma, basal cell carcinoma, and malignant melanoma, or naevi (halo [Sutton] naevi) may show a dense mononuclear infiltrate, composed of T cells or of B cells, sometimes with follicle formation, with polyclonal plasma cells being numerous especially in head and neck localizations.

---

**Fig. 4.74** Lymphadenosis benigna cutis (LABC, B-pseudolymphoma) following tick bite in the earlobe.

**Fig. 4.75** B-PSL. Reactive follicles in lymphadenosis benigna cutis (B-pseudolymphoma).

**Fig. 4.76** Close up view showing follicular centre with tingible-body macrophages featuring a starry sky pattern.

**Fig. 4.77**
- **A** Tingible body macrophages containing ingested nuclear fragments.
- **B** Regular network of CD21+ dendritic cells.
Parapsoriasis

Definition
The term “parapsoriasis” is confusing. It encompasses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling skin lesions. Those diseases which have distinct clinical and histological changes do not fulfill criteria of malignancy, deserve to be labeled with a term which reflects this intermediate situation and labels them as distinct nosologic entities. This term since the days of Brocq has been “parapsoriasis” and there is no reason for changing it. Otherwise there will be a bias in epidemiologic data on frequencies, mortality rates and other parameters.

Two groups of parapsoriasis can be differentiated. The benign form (“parapsoriasis en plaques” [Brocq’s disease]), which never evolves into malignant lymphoma and large plaque forms with or without poikiloderma which after several decades may evolve into mycosis fungoides or CTCL in up to 50% of the cases. Table 4.3 summarizes criteria for differentiation of benign and premalignant forms of parapsoriasis en plaques.

Small plaque parapsoriasis

Synonyms
Parapsoriasis, small patch (digitiform) type (Brocq’s disease); Parapsoriasis en plaques, benign type; digitate dermatitis, xanthoerythrodermia perstans; chronic superficial dermatitis

Epidemiology
This form preferentially occurs in young adults and affects males more frequently than females. There are no statistically reliable data on the incidence, which is estimated less than 0.1 per 100,000 per year. There is little tendency to progress. Survival is not affected since SPP never evolves into malignant lymphoma

Clinical Features
Trunk and upper extremities are preferentially involved. Small (2-5cm in diameter), mostly oval or finger-like patches, slightly erythematous, following skin lines. The color is brown red, and fine and powdery (pityriasiform) scaling may be present. The surface is slightly wrinkled resulting in a pseudoatrophic appearance.

Histopathology
The epidermis is normal or slightly spongicotic with patchy parakeratosis. Patchy loose perivascular and disseminated lymphocytic infiltrate, but no edema, are present in the dermis. Significant epidermotropism of lymphoid cells is lacking.

Immunohistochemistry
Lymphoid cells exhibit mostly CD4+ and some CD8+.

Somatic genetics
Clonal rearrangement for the T-cell receptor genes is not detectable. However clonal rearrangement of lymphoid cells in the peripheral blood of patients has been reported.

Prognosis and predictive factors
The skin lesions are extraordinarily stable in shape and size over years and decades without spreading to extracutaneous localizations. Lymph nodes, peripheral blood, bone marrow or internal organs are not affected. Life expectancy is normal. Progression into mycosis fungoides or other CTCL does not occur.

Fig. 4.78 Parapsoriasis. A Large plaque parapsoriasis with poikiloderma, showing large telangiectatic patches and a netlike pigmentation. B Flattening of the epidermal rete ridges. Band like lichenoid infiltrate. Dilated small blood vessels in the upper dermis.
Parapsoriasis - Large patch type, with or without poikiloderma

Definition
Pre-malignant inflammatory disorder with tendency to evolve into mycosis fungoides. Some authors consider this lesion a manifestation of early cutaneous T-cell lymphoma (CTCL).

Synonyms
Non-poikilodermatous variant. Parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples. Poikilodermatous variant: Prereticuloic poikiloderma, parapsoriasis en grandes plaques poikilodermiques; poikiloderma vasculare atrophicans; parapsoriasis lichenoides; parakeratosis variegata

Epidemiology
All age groups may be affected with a slight male preponderance.

Localization
Breast and buttocks are most commonly involved.

Clinical Features
Few large (more than 5 cm in diameter) patches showing pityriasiform scaling with (poikilodermatous variant), telangiectasia and netlike pigmentation are present. There is no palpable infiltration.

Tumour spread and staging
Lesions may stay unchanged over years and decades, or slowly show enlargement in a few cases. No plaques or tumours occur, except when the disease evolves into CTCL in some of the cases.

Histopathology
Under patchy parakeratosis there is slight atrophy of the epidermis, due to loss of rete ridges, in the poikilodermatous form. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, sparing the papillary region. There is no significant epidermotropism as usually seen in early stages of mycosis fungoides. The poikilodermatous variant of the disease in addition shows dilated blood vessels in the upper dermis.

Somatic genetics
T-cell receptor gamma gene rearrangement, which is clonal in about half of the patients with LPP, is probably without any prognostic significance (2186). Increased telomerase activity and shortened telomere length was also detected in CD4+ T cells from patients with parapsoriasis (2552).

Prognosis and predictive factors
There is no significant difference between the observed and expected survivals in patients with less than 10% skin involved. (2575). However when skin involvement exceeds 10%, as seen in LPP, sporadic cases have an increased risk of transforming into mycosis fungoides after years or decades (2031).

Table 4.0.3
Criteria for distinguishing benign and premalignant forms of parapsoriasis en plaques.

<table>
<thead>
<tr>
<th></th>
<th>Benign form (small patch type)</th>
<th>Premalignant form (large patch type) with or without poikiloderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age distribution</td>
<td>Adults</td>
<td>All ages</td>
</tr>
<tr>
<td>Sex incidence (m:f)</td>
<td>5:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Small (2-5cm in diameter), mostly oval, or finger-like patches, slightly erythematous and wrinkled surface (pseudoatrophy) uniformly pinkish or yellowish with pityriasiform scaling</td>
<td>Few large patches (&gt;5cm in diameter) pityriasiform scaling with or without telangiectases and netlike pigmentation, sometimes slightly hyperkeratotic (parakeratosis variegata)</td>
</tr>
<tr>
<td>Preferential localizations</td>
<td>Trunk and upper extremities</td>
<td>Breast and buttocks</td>
</tr>
<tr>
<td>Histological features</td>
<td>Patchy parakeratosis, slight perivascular patchy infiltrate, no oedema, no significant epidermotropism</td>
<td>Slight epidermal atrophy with loss of rete ridges, significant band-like dermal lymphocytic infiltrate sparing the subepidermal zone, no significant epidermotropism, no oedema; telangiectases may be prominent in the poikilodermatous variant</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Life expectancy normal; no progression to mycosis fungoides</td>
<td>Life expectancy normal in most cases; progression to mycosis fungoides occurs</td>
</tr>
</tbody>
</table>
Langerhans cell histiocytosis

Definition
Langerhans cell histiocytosis (LCH) is a clonal disorder with systemic spread, characterized by proliferation of dendritic cells which bear morphologic and phenotypic markers of Langerhans cells, characterized by Birbeck granules and expression of CD1a and S-100.

ICD-O code
9751/1

Synonyms
Histiocytosis-X, Langerhans cell granulomatosis, Langerhans cell disease

Epidemiology
LCH predominantly occurs in infants. Median age at diagnosis is 3-5 years (2,299). It has also been reported in patients up to the ninth decade of life (1551,1578,1941), and occurs equally in men and women. The incidence has been estimated as 0.1–0.5 per 100,000 population per year. There have been reports on familiar cases with autosomal recessive inheritance.

Etiology
The etiology is unknown. Different groups have studied female patients with cutaneous LCH using a variety of x-linked polymorphisms to demonstrate clonality (2530,2574). In some cases, association with lymphomas, leukaemias and lung tumours (666) has been observed; in others, infections and environmental factors, including El Nino, have been related to childhood LCH (455). Many view LCH as reactive process (716,2583) because of its tendency toward spontaneous remission and response to mild, non-toxic therapy.

Localization
Two thirds of the sites of involvement diagnosed throughout the course of the disease are present at diagnosis (2). Initial bone involvement is found in almost all patients. Other organs involved skin (25-100%, depending on subtype), ear, liver, lung, and lymph nodes (299).

Clinical Features
The clinical presentation of LCH is very diverse and depends on the subtype. Skin lesions may be seen either as single organ involvement or as part of a multiorgan systemic disease in 25-100% of cases. Any anatomic site can be involved including scalp, nails, palms and soles as well as mucous membranes.

Letterer-Siwe Disease
This is the most severe, disseminated form of Langerhans cell histiocytosis. It affects children in their first year of life but occurrence in adults has been reported (1731). Tiny (0.5 mm in diameter) rose-yellow or brownish-red, translucent papules and patches are found on the scalp, diaper and seborrhoeic sites like nasolabial folds, perioral region, and on the upper trunk. In time, the papules become scaly and crusted and may coalesce into plaques. Petechial and purpuric lesions, pustules and vesicles as

Table 4.04
Langerhans cell histiocytoses and their characteristics. This classification has limitations because of the highly variable manifestations of the disease with many overlapping features (340).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age</th>
<th>Skin involvement</th>
<th>Clinical Features</th>
<th>Course</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letterer Siwe</td>
<td>First years of life</td>
<td>~90-100%</td>
<td>Fever, weight loss, lymphadenopathy, hepatosplenomegaly, pancytopenia, bone lesions</td>
<td>Acute</td>
<td>Mortality rate: 50-66%</td>
</tr>
<tr>
<td>Hand-Schüller Christian</td>
<td>Children adults</td>
<td>~30%</td>
<td>Osteolytic bone lesions, diabetes insipidus exophthalmos, otitis</td>
<td>Subacute to chronic</td>
<td>Mortality rate: &lt;50%</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>Mainly adults</td>
<td>&lt;10%</td>
<td>Solitary bone or skin lesions</td>
<td>Chronic</td>
<td>Favorable</td>
</tr>
<tr>
<td>Congenital self-healing reticulohistiocytosis (CSHR)</td>
<td>Congenital adults</td>
<td>100%</td>
<td>Skin lesions only</td>
<td>Self healing</td>
<td>Excellent*</td>
</tr>
</tbody>
</table>

*Both relapses and conversion to systemic disease can occur, so long-term follow-up is needed (1369).
Nodules are uncommon, but may be found on the trunk and tend to ulcerate. Additional symptoms include fever, weight loss, rash, lymphadenopathy, hepatosplenomegaly, pancytopenia and purpura.

**Hand – Schüller - Christian disease**

The typical triad includes osteolytic skull lesions (100%), hypopituitarism induced diabetes insipidus (50%), and exophthalmos (10%). Otitis media, generalized lymphoadenopathy, hepatosplenomegaly, and pulmonary disease may be additional findings.

Skin lesions occur in about 30% of cases, usually in the intertriginous areas, most often as papules and nodules which may be ulcerated, erosive and superinfected.

**Eosinophilic granuloma**

The most common site of involvement is bone. The uncommon cutaneous lesions are deep dermal or subcutaneous nodules which are not clinically distinct (818,1956). Lesions have to be differentiated from granuloma eosinophilicum faciei, a chronic variant of leukocytoclastic vasculitis with variable presence of eosinophils, but usually no extracutaneous manifestation (452).

**Congenital self-healing reticulo-histiocytosis (CSHRH)**

CSHRH (synonyms: Hashimoto-Pritzker disease; congenital reticulohistiocytosis; congenital self-healing Langerhans cell histiocytosis) (981,2082) is a rare condition (5% of all LCH), initially seen at birth or in the neonatal period, with solitary, localized to generalized papules, vesicles, or nodules on the trunk, head, palms and soles, sometimes showing central ulceration (217). The skin lesions tend to involute spontaneously within weeks to months leaving behind hypo- or hyperpigmented macules or patches (979,1372). Affected infants are otherwise well (1369). Patients should be carefully followed since relapses may occur, including bone involvement, and the occasional case may progress to Letterer-Siwe disease (1445). Some cases of CSHRH may be clinically confused with the blueberry muffin syndrome, congenital leukaemic infiltrates, xanthogranulomas or mast cell disease, but the microscopic picture brings clarity (360).

**Histopathology**

The hallmark and unifying feature of all variants of LCH is a cell with large, pale, folded or lobulated, often reniform, vesicc-
ular nucleus and abundant, slightly eosinophilic or amphophilic cytoplasm. Nucleoli are not prominent. Histological variations correlate with the clinical appearance of the lesions. Features may be predominantly proliferative in Letterer-Siwe disease, xanthomatous in Hand-Schüller-Christian-disease, granulomatous as in eosinophilic granuloma, or “reticulocytic” with abundant eosinophilic cytoplasm (ground glass appearance of giant cells) in Hashimoto-Pritzker disease. Fully developed papules and plaques show a dense band-like infiltrate obscuring the dermo-epidermal junction. Epidermotropism of LCs with intraepidermal microabscess formation can be found. In addition to LCs and eosinophils, the infiltrate may contain variable numbers of lymphocytes, epithelioid macrophages including foam cells and giant cells, neutrophils, plasma cells, and extravasated erythrocytes.

**Immunohistochemistry**
The phenotypic hallmarks in LCH are expression of CD1a, CD4 and S-100 protein, while macrophage markers, including CD68 and lysozyme, are usually negative.

**Electron microscopy**
Rod- or rocket-shaped granules measuring 200-400 nm (Birbeck granules, Langerhans cell granules) are the ultrastructural hallmark of LCs. The number of Birbeck granules varies, with usually greater prominence in early lesions. Coexistence of myelinoid laminated inclusions or “vermiform” bodies (1372) and Birbeck granules is common in CSHRH.

**Genetics**
A variety of inconsistent cytogenetic abnormalities have been found in several patients with LCH studied so far using comparative genomic hybridization, loss of heterozygosity (LOH) and other techniques (107, 227, 848, 1666). Heterogeneous overexpression of TGFbeta receptor I and II, MDM2, p53, p21, p16, Rb, and BCL2 has been detected in lesional LCH cells (2097). Familial clustering of two different manifestations of LCH support a role for genetic factor(s) in LCH and raise the possibility of inherited mutations that promote emergence of clonal Langerhans cells (93, 134, 1200). LCH may follow percursor T-cell acute lymphoblastic leukaemia, and in such cases a clonal relationship has been shown for T-cell receptor gene rearrangements (720).

**Prognosis and predictive factors**
The biologic behaviour of LCH ranges from spontaneous remission to lethal dissemination, and such behaviour cannot be predicted on the basis of histologic features (1941). The presence and degree of organ dysfunction, age less than 1 year at diagnosis (except the Hashimoto-Pritzker type), male sex, progressive episodes, and the absence of response to therapy are the most reliable indicators of prognosis (2, 1019). In general, about 10% of patients with multifocal disease die, 30% undergo complete remission, and the remaining 60% embark upon a chronic course (1065, 1425).
Indeterminate cell histiocytosis

Definition
Indeterminate cell histiocytosis (ICH) is a proliferative cutaneous disorder of the so-called “indeterminate cells” (IC), i.e. distinct dendritic cells of the skin that display histological, ultrastructural and antigenic features similar to those of Langerhans cells, but do not contain Birbeck granules.

Epidemiology
The disease is very rare (about 15 cases described up to 2003), usually occurs during adulthood, although two cases were in teenagers (1621,2019) and two cases in children (1413,1524). Both sexes have been affected.

Etiology
The origin of indeterminate cells is still debated. Indeterminate cells may derive from an arrest of Langerhans cell migration and maturation (1302), may represent precursors of Langerhans cells which acquire Birbeck granules as they transit from dermal to epidermal sites (1499). Furthermore it has been suggested (222) that indeterminate cells represent members of the epidermal/dermal dendritic cell system which migrate from skin to regional lymph nodes. According to this concept, indeterminate cell histiocytosis can be considered a disorder due to locally arrested dermal indeterminate cells proliferating prior to their departure for lymph nodes.

Localization
Lesions are usually restricted to the skin. Solitary lesions have been described on the trunk and arms, while multiple lesions are widespread.

Clinical features
The eruption consists of a solitary nodular lesion (222,279,1413,1621) or of multiple papulonodules (279,531,1499,2019,2179).
Solitary nodules are soft, red in colour and about 1 cm in diameter, and may be ulcerated. Multiple lesions are firm, asymptomatic papulonodules ranging in size from a few millimetres to 1 cm, varying in colour from dark-red to brownish, and covered by intact skin. These lesions appear in successive crops. Mucous membranes are always spared. Visceral involvement has been observed only in a child. Patients are in good general health.

Histopathology
Light-microscopic evaluation reveals an infiltration of histiocytic cells in the whole dermis and sometimes within the epidermis. The proliferating cells show an abundant pale eosinophilic cytoplasm and large irregular folded or twisted nuclei.
A few mitotic figures and multinucleated giant cells may be observed. Clusters of lymphocytes are admixed.

Immunohistochemistry
Proliferating cells are weakly positive for CD1a, CD68 (KP1), CD11c (Leu M5), CD14 (OKM1), factor XIIIa, lysozyme, α1-antitrypsin, HLA-DR, but negative for CD207 (langerin) (1302,1499,1524,1621,2179).

Electron microscopy
The proliferating cells reveal an indented nucleus and an abundant cytoplasm with lysosomes, phagosomes and a well-developed endoplasmic reticulum. Birbeck granules are absent (222,531,1413).

Prognosis and predictive factors
Most cases have exhibited complete or partial spontaneous regression of lesions without recurrences. Two cases displayed malignant behaviour (279,1524). The prognosis is reasonably good, but leukaemia may be associated with this disease (279,1302).
Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

**Definition**
Sinus histiocytosis with massive lymphadenopathy is a reactive condition of unknown etiology, characterized by a proliferation of histiocytes which usually exhibit emperipolesis of lymphocytes. The disease can mimic lymphoma. Extranodal involvement is frequent.

**Synonyms**
Sinus histiocytosis with massive lymphadenopathy, Rosai-Dorfman disease

**Epidemiology**
Sinus histiocytosis is a rare non-neoplastic disease. Lymph nodes are predominantly affected in children and young male adults; the cutaneous form is particularly seen during the third and fourth decades in female patients (74,307,483).

**Etiology**
The etiology is unknown. Lesions are polyclonal, probably the consequence of a cytokine dysregulation (1603).

**Localization**
Cervical lymph node involvement is most characteristic. Cutaneous lesions frequently occur on the head and neck, mucous lesions (1105,2498) in the nose and paranasal sinus. Extranodal disease may also affect any other organ (2455).

**Clinical features**
Children with massive cervical lymph node swellings frequently suffer from fever and malaise. Laboratory tests show leukocytosis, anemia, polyclonal hypergammaglobulinaemia and an accelerated erythrocyte sedimentation rate. Extranodal involvement is common, up to 40%. Pure cutaneous forms are rare; solitary, clustered or wide-spread, red to brownish papules, rarely plaques and nodules are seen. Regression leaves atrophic, brown macules.

**Histopathology**
Lymph node architecture is replaced by sheets of faintly stained (“clear”) to slightly eosinophilic macrophages. In extranodal location infiltrates frequently simulate lymph node sinuses (“sinusoidal pattern”). Emperipolesis of lymphocytes, erythrocytes or other nuclear debris is prominent, but not specific; it can also be seen in, e.g., subcutaneous T-cell lymphomas. Lymphocytes, plasma cells, neutrophils and fibrosclerosis are found to a variable degree.

**Immunohistochemistry**
Macrophages are positive for CD68 (PGM1, KP1) and S100 protein; CD1a, factor XIIIa and CD34 are negative (1796).

**Electron microscopy**
Macrophages ingest intact lymphocytes. Phagolysosomal structures, but no Birbeck granules are found.

**Prognosis and predictive factors**
Manifestation in children and lymph node involvement are more readily and rapidly associated with regression than in adults and spread to extranodal sites. The vast majority of lesions is self-limited and benign. Rare fatalities have been associated with immunologic disorders, lymphomas of Hodgkin and non-Hodgkin type, leukaeemias (62), and exceptional cases with solid tumours (1900).

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![Fig. 4.86](image-url) Sinus histiocytosis with massive lymphadenopathy. A Left: Brownish nodule of sinus histiocytosis on the nose. B Right: Clustered brownish papules of sinus histiocytosis on the trunk. C Left: Sheets of macrophages in sinus histiocytosis positive for $S100$ protein. Right: Lymphocytes within cytoplasm of histiocytes, i.e., emperipolesis.
Juvenile xanthogranuloma

Definition
Juvenile xanthogranuloma (JXG) is a benign, self-healing, non-Langerhans-cell (LC) histiocytosis most frequently seen in infants and children, characterized by yellowish asymptomatic papules and/or nodules located in the skin and other organs and consisting of an infiltrate of macrophages with a variable degree of lipidization in the absence of a metabolic disorder.

Synonyms
Xanthoma multiplex (33); Nevoxanthoendothelioma (1551).

Epidemiology
JXG is the most common form of non LC histiocytosis (378,824). JXG appears within the first year of life in about 75% of cases; in 15-30% it is present at birth.

Etiology
The etiology is unknown. Foamy cells constitute the main part of the mature lesions of JXG and accumulate lipids, despite normal levels of plasma lipids. It has been suggested (208) that the uptake of low-density lipoprotein cholesterol and the biosynthesis of intracellular cholesterol are both enhanced; such enhancement might play a role in the process of accumulation of cholesterol esters in the macrophage.

Localization
Cutaneous lesions are irregularly scattered throughout the skin without a tendency to cluster, and are mainly located on the upper part of the body (378,824). Mucous membranes may rarely be involved.

The most common extracutaneous manifestation of JXG (occurring mainly in the papular and subcutaneous (256) forms) is ocular involvement (256,614,2045, 2603). Ocular lesions may occur in about 1-10% of affected children and are almost always unilateral and may lead to haemorrhage and glaucoma. Such lesions may precede or follow the cutaneous lesions. The nodular variant of JXG may occasionally be related to systemic lesions of lungs, bones, kidneys, pericardium, colon, ovaries, testes and central nervous system (378,824,2536).

Clinical features
Two main clinical variants can be distinguished: a papular form and a nodular form (824).

The papular form is the most frequent and is characterized by numerous (up to 100), firm hemispheric lesions, 2-5 mm in diameter, that are red-brown at first and then quickly turn yellowish. These lesions are associated in perhaps 20% of patients with café-au-lait spots of neurofibromatosis (1140) and may be related to juvenile chronic myeloid leukaemia (538,1650).

The nodular form is less frequent, and is marked by one or a few lesions. The nodules are round to oval, 1-2 cm in diameter, high-domed, shiny, translucent, yellowish or red brown and sometimes show telangectasias on their surface. The term giant JXG has been used to indicate lesions larger than 2 cm. Unusual clinical variants (378,383) are the mixed form (simultaneous presence of both papules and nodules) and the form en plaque, a group of JXG lesions with a tendency to coalesce into a plaque as the only expression of the disease.

Histopathology
Early lesions are characterized by a dense infiltrate of monomorphous, non-lipid containing, macrophages with abundant, slightly eosinophilic, cytoplasm (378,824). With time the cytoplasm of macrophages becomes laden with lipid and appears foamy. Mature lesions contain foamy cells, for-
eign body giant cells and Touton giant cells, mainly distributed in the superficial dermis and on the border of the infiltrate. In addition to macrophages and foamy cells, there may be lymphocytes, eosinophils, neutrophils and plasma cells scattered throughout the lesion. In older lesions fibrosis replaces the cellular infiltrate, and lipids are not present extracellularly.

Immunohistochemistry
Immunohistochemically (824, 2049) macrophages and Touton cells show a uniform positive staining with CD14, CD68, HAM56 (markers with specificity for macrophages) and vimentin, frequent positive staining for factor XIII (markers of dermal dendrocytes) and for cathepsin B and occasional staining for MAC387 (a marker for monocytes and macrophages). S100 protein, CD1a (OKT6), CD15 (Leu M1) and peanut agglutinin (PNA) are not usually expressed on the macrophages of JXG.

Electron microscopy
Under the electron microscope (378, 824), the macrophages that characterize the early stage of the disease exhibit pleomorphic nuclei, are rich in pseudopods, and contain many elongated and irregular dense bodies. Clusters of comma-shaped bodies, but no Langerhans granules (LG) can occasionally be observed. In older lesions there is a predominance of foamy cells, the cytoplasm of which is completely filled with lipid vacuoles, cholesterol clefts, and myeloid bodies. The cells corresponding to Touton giant cells are large (150-250 µm) and sometimes contain more than 10 nuclei. At their periphery, such cells are rich in lipid material, whereas in their centre, mitochondria and lysosomes predominate.

Genetics
JXG is not linked to any genetic locus, but the association with café-au-lait spots of neurofibromatosis (NF1) (2536) and the occasional association with neurilemmomatosis (NF2) (1115) suggests that a JXG locus could reside on chromosome 17q11.2 or 22q12. Clinical (1115) and genetic analyses (1056) indicate that neurilemmomatosis and neurofibromatosis type 2 (NF2) genes are identical.

Prognosis and predictive factors
The papules and nodules of the skin tend to flatten with time and both the skin and most of the visceral lesions disappear spontaneously within 3-6 years. A few cases of JXG with fatal evolution, probably due to central nervous system involvement (378) or fatal liver disease (614), have been reported. In JXG periodic complete blood count and peripheral smears would be judicious during a patient’s first two years of life, which is the time of the peak incidence for juvenile chronic myeloid leukaemia.
Reticulohistiocytosis

Definition
Reticulohistiocytosis of the skin represents a spectrum of rare clinical entities, ranging from the solitary cutaneous form (SCR) through the generalized cutaneous form without systemic involvement (GCR), to multicentric reticulohistiocytosis with systemic involvement (MR). The skin lesions in all these conditions demonstrate an identical histological pattern, characterized by numerous mononucleated or multinucleated macrophages with abundant, eosinophilic, homogeneous to finely granular cytoplasm with a characteristic ground-glass appearance.

Synonyms
Giant cell reticulohistiocytosis, giant cell histiocytosis; cutaneous reticulohistiocytoma, reticulomatosis with giant cell histiocytes; normocholesterolemic xanthomatosis; lipoid dermatitis; lipoid rheumatism; multicentric reticulohistiocytosis; non-diabetic cutaneous xanthomatosis; reticulohistiocytic granuloma; reticulohistiocytosis of the skin and synovia.

Epidemiology
Reticulohistiocytosis mostly occurs in adults over 40 years of age, but the disease may appear during adolescence: SCR and GCR have been also observed in children. In adults, the most frequent variant is MR, with about 50 and GCR with 10 patients reported in the literature.

There is no preference for either sex (167,465,1405,1462).

Etiology
The etiopathogenesis is unknown. Reticulohistiocytosis may represent an abnormal macrophage response to different stimuli. In solitary forms, local trauma such as insect bites, folliculitis or ruptured infundibular cysts may play a role (379), while in systemic forms the association with autoimmune disorders and internal malignancies suggests an immunological basis for the initiation of this reaction (1752).

Localization
SCR involves mainly the head and the neck, but may be found in any cutaneous site (382,1082). In GCR the lesions are widely scattered on the skin (381,547,847,2363). In MR (167,413,465,1405,1752) skin lesions preferentially affect the fingers, the palms and the back of the hands, the juxta-articular regions of the limbs and the face. Oral, nasal and pharyngeal mucosa are involved in 50% of cases. Osteoarticular lesions involve mainly the hands (80%), knee (70%) and wrists (65%).

Clinical features
The solitary cutaneous reticulohistiocytosis (SCR) or reticulohistiocytoma cutis (382,1082) is characterized by a single, firm, rapidly growing nodule varying in colour from yellow-brown to dark-red.

The lesion is often clinically misdiagnosed, it occurs without evidence of systemic involvement, and its onset may be preceded by trauma.

Generalized cutaneous histiocytosis (GCR) (381,547,847,2363) is a purely cutaneous form characterized by the eruption of firm, smooth, asymptomatic papulonodular lesions, 3-10 mm in diameter. The colour of the recent lesions is pink-yellow, while the older lesions show a red-brown colour. Joint and visceral lesions are absent. Possibly, this purely cutaneous form could represent an early stage of multicentric reticulohistiocytosis, before the appearance of joint or visceral lesions.

The term multicentric reticulohistiocytosis (167,413,465,1405,1752) is used to indicate a form of reticulohistiocytosis characterized by the association of a cutaneous and mucous membrane papulonodular eruption with severe arthropathy and other visceral symptoms. The papulonodular lesions range in diameter from a few mm to 2 cm, and are round, translucent and yellow-rose or yellow-brown in colour. Grouping of lesions into plaques can give a cobblestone appearance, but lesions are mostly scattered and isolated. They do not tend to ulcerate, and are pruritic in about one-third of cases. Osteoarticular manifestations cause severe chronic polyarthritis with arthralgias, and are the initial sign of the disease in about 5-65% of cases (167,465,1405). The osteoarticular lesions

Fig. 4.91 Multicentric reticulohistiocytosis. A Purplish-brown, firm nodules characteristically affect the fingers. Periungual papules are arranged about the nail folds. B Papulonodular lesions are spread on the face, lips and oral mucosa. Mucous membranes are involved in about 50% of cases. C Symmetrical involvement of the knees. In this patient, osteoarticular manifestations were the initial sign of the disease. From: R. Caputo (378)
show a progressive destructive course of 6-8 years, and then become stable. Other systemic localizations, histopathologically documented are very rare. Muscular (667) (myositis, myotonia and myoatrophy), cardiopulmonary (532) (pericarditis, cardiac insufficiency, pleuritis, pulmonary infiltration), ocular (667) (exophthalmos, conjunctival infiltration), gastric (gastric ulcer), thyroid (thyroid nodules) and submandibular salivary gland involvements have occasionally been reported. Fever, weight loss and weakness can be present. In MR there is an association with a variety of autoimmune disorders such as dermatomyositis, lupus erythematosus, or Hashimoto thyroiditis as well as internal malignancies in 15-27% of cases (167,413,1405,1752). Solid tumours such as bronchial, breast, stomach and cervical carcinomas are most common. Lymphomas and myelodysplastic syndromes have been found less frequently.

**Histopathology**

The histological findings in the three types of reticulohistiocytosis and in the different tissues are identical (167,465,1405,1462). Early lesions are composed of macrophages and lymphocytes, and therefore may be confused with other histiocytes of the skin. Older lesions show the characteristic histological pattern: the presence of numerous large, mononuclear or multinucleated macrophages with an abundance of eosinophilic, homogeneous to finely granular cytoplasm having a ground glass appearance. At times, phagocytosis of connective tissue and/or cellular components may be seen (379,532). Histochemically, the granular material in macrophages and giant cells stains with periodic acid-Schiff, Sudan black and scarlet red, indicating the presence of glycolipids and/or glycoproteins and neutral fat (167).

**Immunohistochemistry**

Macrophages stain with macrophage markers KP1/PGM1 (CD68), Ki-M1p, and for the mesenchymal epitope of vimentin, and show variable reactivity with HAM56 and for factor XIIa, lysozyme and α1-antitrypsin (381,382,424,2027,2585). In contrast, these cells are usually negative for CD1α, S100 protein, Leu-M1 (CD15) and MAC387. Rare exceptions have been reported. According to Zelger et al. (2585), SCR differs histopathologically and immunohistochemically from MR as lesions are better circumscribed, multinucleated giant cells more prominent, gigantic and bizarre, and macrophages regularly negative for factor XIIa in the former entity.

**Electron microscopy**

The infiltrate is formed by large mononuclear to multinucleated cells exhibiting numerous peripheral villi (532,667). Nuclei are irregular and often polylobated, with nucleoplasm of medium electron density and one or two nucleoli. The cytoplasm contains one or more Golgi apparatus, and is rich in mitochondria, lysosomes, dense bodies, phagosomes and myelin figures. The cytoplasm of about 5-40% of the cells of the infiltrate in many cases contains the so-called pleomorphic cytoplasmic inclusions (380-382,532), varying in number from cell to cell. The pleomorphic cytoplasmic inclusions are unique and highly complex structures consisting mainly of unit membranes, occasionally surrounding electron-dense areas containing vesicles. Birbeck granules are absent. About 20% of all macrophages show collagenophagic activity (379,766), but not pleomorphic cytoplasmic inclusions.

**Prognosis and predictive factors**

The purely cutaneous forms of reticulohistiocytosis (solitary and generalized) may involute spontaneously (382,847). It is possible that the generalized purely cutaneous form is an early stage of MR, before the appearance of joint and visceral lesions (381,847). In MR, there is no parallelism between the mucocutaneous and articular manifestations. The mucocutaneous lesions have an unpredictable course, and may remit spontaneously. In half of the patients, the osteoarticular manifestations become stable, while in the other half, they show a progressive destructive course (1405). The prognosis is favourable for the cutaneous forms. The prognosis of MR is related to the importance of the osteoarticular manifestations and of the underlying immunologic disorders and neoplasms.

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Fig. 4.92 Reticulohistiocytosis. A Conventional microscopy: the histological pattern of the lesions is characterized by the presence of numerous, large, mononucleated histiocytes with an abundant eosinophilic, finely granular cytoplasm. B Conventional microscopy: in these giant cells showing leukocyte phagocytosis, the typical ground-glass appearance of the cytoplasm is evident. C Conventional microscopy: Weigert-Van Gieson staining. Collagen phagocytosis is an occasional finding.
**Mastocytosis**

**Definition**
Mastocytosis is a heterogeneous group of disorders characterized by the abnormal growth and accumulation of a clone of mast cells in one or more organ system (1448). Most patients have cutaneous mastocytosis (CM) with indolent disease that is confined to the skin and that may regress spontaneously. A minority of patients, usually adults, have systemic mastocytosis (SM) that may rarely be highly aggressive and associated with multi-system involvement and short survival time, or that may be associated with non-mast-cell haematopoietic malignancies (1450, 2372,2405).

**ICD-O Codes**
- Cutaneous mastocytosis (CM); maculopapular or plaque type mastocytosis, formerly urticaria pigmentosa (UP); telangiectatic mastocytosis, formerly telangiectasia macularis eruptiva perstans (TMEP); diffuse cutaneous mastocytosis (DCL); solitary mastocytoma (965,2405)
- Indolent systemic mastocytosis 9740/1
- Aggressive systemic mastocytosis 9741/3
- Mastocytosis with associated haematopoietic disorder 9741/3
- Mast cell leukaemia 9742/3

**Synonyms**
- Mast cell disease; mast cell proliferative disease

**Epidemiology**
Cutaneous mastocytosis may be present at birth and usually first appears before six months of age. A second peak incidence is found in young adults in their 3rd and 4th decades. Paediatric mastocytosis usually regresses by adolescence. Adult mastocytosis is more likely to be persistent and may be associated with SM, rarely also with aggressive systemic mastocytosis. There is no clear gender or ethnic predominance of cases (964,1450).

**Etiology**
The KIT protein is a receptor tyrosine kinase that is also known as the mast cell growth factor receptor. Adult mastocytosis and rare pediatric cases are associated with somatic mutations in the c-KIT proto-oncogene that alter the enzymatic site of the KIT protein (361,1449). Rare kindreds with familial mastocytosis have germ line c-KIT mutations that affect regulatory portions of the KIT protein, also causing constitutive kinase activation. These patients may also have gastrointestinal stromal tumours (GISTs) which are known to be caused by regulatory type c-KIT activating mutations (189,

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Fig. 4.94 Cutaneous mastocytosis. A Wheal and flare of Darier sign. The skin lesions of all forms of cutaneous mastocytosis may urticate when stroked. A palpable wheal appears a few moments after physical stimulation, due to histamine from the mast cells. B Tense blister containing clear fluid on skin of infant with diffuse cutaneous mastocytosis. The skin may appear thickened and reddish brown with diffuse involvement. Note the blister caused by mast cell degranulation and histamine release. Blister may form in infants because the dermal-epidermal junction is not yet well developed. C Large pigmented papules of paediatric urticaria pigmentosa. D Reddish brown macules, patches and plaques on abdomen and arm of an adult with cutaneous and systemic mastocytosis. E Telangiectasia macularis eruptiva perstans form of cutaneous mastocytosis in an adult. F Pigmented macules of adult type urticaria pigmentosa. The number of lesions may range from a few to thousands.
Patients with extensive involvement may have tachycardia, and respiratory symptoms. Hypotension including anaphylaxis, flushing, and cramping may be seen in infants whose dermo-epidermal junction is not well developed so that overlying lesions of any form of cutaneous involvement may present an exaggeration of Darier sign. Clinical normal skin may also urticate when stroked, (so-called dermographism). Moderate itching is present in about half of the patients (579). Most cutaneous lesions show an increase in epidermal melanin pigment which, combined with the tendency of these lesions to urticate, has led to the term “urticaria pigmentosa”, a historic designation that has recently been proposed to be abandoned (2405). Stroking of any lesion of CM may cause mast cell degranulation with localized swelling or urtication (Darier sign).

Histopathology

In haematoxylin and eosin (H&E) stained sections, normal mast cells have moderately abundant, oval or polygonal shaped cytoplasmic granules with round to oval nuclei, sometimes giving the appearance of a “fried egg”. The nuclei have clumped chromatin and indistinct or inapparent nucleoli. The cytoplasmic granules are filled with small, faintly visible, eosinophilic or amphiphilic granules which stain metachromatically purple.

The clinical presentation of CM may range from subtle diffuse erythema to grossly evident, widespread doughy dermal thickening with accentuation of cutaneous surface markings, giving a so-called “grain leather”, (peau chagrine) or orange skin (peau d’orange) appearance (964,1449,1450,2430,2525). Tense blisters filled with clear fluid, occasionally slightly-tinged with blood, may be seen overlying lesions of any form of cutaneous mastocytosis in infants. Individual lesions in young children tend to be lightly pigmented and occur as solitary nodules or multiple papules, or rarely as large heavily pigmented macules, large plaques, or diffuse infiltration of the skin (964).

In normal skin, individual mast cells are found perivascularly and scattered throughout the dermis, without formation of clusters. Mast cells in mastocytosis also tend to accumulate perivascularly, and are most often evident in the super-
ficial dermis, within the dermal papillae (1401,1607). In solitary mastocytomas and papular, nodular, or diffuse CM, the papillary and/or reticular dermis may show either scanty increases in mast cell numbers or heavy mast cell infiltrates, and there may be extension into the subcutaneous fat. In CM, individual mast cells may rarely be found in the lower epidermis. Unequivocal diagnosis of cutaneous mastocytosis requires the demonstration of aggregates of mast cells within the dermis, and this may be difficult and require multiple biopsies in the TMEP form of adult mastocytosis.

Lesions of mastocytosis are usually composed of an infiltrate of monomorphous mast cells, and rarely observed infiltrating eosinophils should raise the possibility of dermal hypersensitivity reaction, parasitosis or an arthropod bite.

**Histogenesis**

Mast cells are derived from CD34+ haematopoetic precursor cells (1982).

**Somatic genetics**

Mastocytosis is a clonal disease in both adults and children (1448,1449). The tumour cells of almost all cases of adult onset sporadic disease carry somatic point mutations of c-KIT that change the enzymatic site of the KIT protein, causing constitutive activation (361,1449). Paediatric sporadic mastocytosis has also been shown to be clonal, but c-KIT activating mutations are rare (361,1449). Very rare cases of familial mastocytosis, usually associated with GISTs tumours, are associated with germ line c-KIT mutations that activate KIT by affecting regulatory portions of the molecule, rather than the enzymatic site (189, 1447).

**Prognosis and predictive factors**

Patients with mastocytosis confined to the skin generally have a good prognosis, and cutaneous involvement is usually an indicator of a relatively better prognosis in SM. CM in paediatric patients with solitary mastocytomas or typical papular and macular rashes usually regress by adolescence. The presence of enzymatic site type KIT activating mutations may indicate persistent disease in this population, and classification of mastocytosis based on both clinical and molecular genetic features may eventually prove to be both prognostically and therapeutically useful (1446, 1465). In adults, although CM may be symptomatic and persist, overall survival is usually not adversely affected, even in the face of concomitant systemic involvement. Patients having aggressive variants of SM, however, may have a rapidly progressive downhill course with survival measured in months. In patients with associated haematologic malignancies, the prognosis is determined by the course of the related haematologic disease (964).

**Immunohistochemistry**

Mast cells are bone-marrow derived cells and therefore express CD45 (CLA). They also express CD117 (the KIT protein) and HLA-DR. Relatively specific mast cell markers include highly sulfated glycosaminoglycans like heparin (toluidine blue stain), tryptase and chymase. CD-2 and/or CD25 may be aberrantly expressed in mast cells of SM (934, 2404, 2405).
CHAPTER 5

Soft Tissue Tumours

Most soft tissue tumours are benign, outnumbering malignant ones by about 100 to 1. Soft tissue sarcomas comprise over 50 histological types, many of which have more than one subtype. Their behaviour varies from indolent to very aggressive, with consequent variation in survival, according to histological type, grade, and sometimes genetic constitution, but the overall 5 year survival is about 65-75%. In general, sarcomas in skin or subcutis have a more favourable outcome than those located beneath deep fascia. Only those tumours with a predilection for the skin, and not already covered in the WHO Classification of Tumours of Soft Tissue and Bone are described in this chapter.
**WHO histological classification of soft tissue tumours**

### Vascular tumour
- Haemangioma of infancy 9131/0
- Cherry haemangioma 9120/0
- Sinusoidal haemangioma 9120/0
- Hobnail haemangioma 9120/0
- Glomeruloid haemangioma 9120/0
- Microvenular haemangioma 9120/0
- Angiolympoid hyperplasia with eosinophilia 9119/0
- Spindle cell haemangioma 9136/0
- Tufted angioma 9161/0
- Arteriovenous haemangioma 9123/0
- Cutaneous angiosarcoma 9120/3

### Lymphatic tumours
- Lymphangiomatosis circumscriptum 9170/0
- Progressive lymphangiomatosis 9170/0

### Smooth and skeletal muscle tumours
- Pilar leiomyoma 8890/0
- Cutaneous leiomyosarcoma 8890/3

### Fibrous, fibrohistiocytic and histiocytic tumours
- Dermatomyofibroma 8824/0
- Infantile myofibromatosis 8824/1
- Sclerotic fibroma 8823/0
- Pleomorphic fibroma 8832/0
- Giant cell fibroblastoma 8834/1
- Dermatofibrosarcoma protuberans 8832/3
- Dermatofibroma (fibrous histiocytoma) 8832/0

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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (786) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

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**TNM classification of soft tissue sarcomas**

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>G Histopathological Grading</th>
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<tbody>
<tr>
<td>TX: Primary tumour cannot be assessed</td>
<td>* * * *</td>
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<tr>
<td>T0: No evidence of primary tumour</td>
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<tr>
<td>T1: Tumour ≤ 5 cm in greatest dimension</td>
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<tr>
<td>T1a: superficial tumour*</td>
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<tr>
<td>T1b: deep tumour</td>
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<tr>
<td>T2: Tumour &gt; 5 cm in greatest dimension</td>
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<tr>
<td>T2a: superficial tumour</td>
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<tr>
<td>T2b: deep tumour</td>
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<tr>
<th>Regional lymph nodes (N)</th>
<th>Stage grouping</th>
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<tbody>
<tr>
<td>NX: Regional lymph nodes cannot be assessed</td>
<td>* * * *</td>
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<tr>
<td>N0: no regional lymph node metastasis</td>
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<tr>
<td>N1: regional lymph node metastasis</td>
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Notes: Regional node involvement is rare and cases in which nodal status is not assessed either clinically or pathologically could be considered N0 instead of NX or pNX.

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>Stage IV</th>
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<tr>
<td>M0: no distant metastasis</td>
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<tr>
<td>M1: distant metastasis</td>
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*From references 892, 2219.*

Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are classified as deep tumours.
Soft tissue tumours: Introduction

Epidemiology
Age-standardized incidence rates of soft tissue sarcomas, which are fairly constant in most areas covered by cancer registration, range from 1-3 per hundred thousand population {1781}. Sarcomas of cutaneous origin are relatively rare, and are far outnumbered by carcinomas, melanoma and benign mesenchymal neoplasms of skin and subcutis (superficial soft tissue). The most common benign tumours are lipomas, fibrous histiocytomas, vascular or smooth muscle lesions including angioleiomyomas, and nerve sheath tumours (schwannoma, neurofibroma). Some of these tumours are covered elsewhere {756}. The vast majority are located superficially and do not exceed 5 cm in diameter. Sarcomas are mostly found in older adults. They arise mainly in the extremities, especially the thigh, followed by trunk, head and neck and retroperitoneum.

Etiology
Most soft tissue sarcomas arise spontaneously and are of unknown etiology. A small number arise in rare familial cancer syndromes with germline mutations. A number of other congenital and inherited syndromes are associated with benign and malignant soft tissue tumours; type examples include Mafucci syndrome (chondroid and vascular tumours) and Cowden disease (lipomas, haemangiomata). Further details can be found in the WHO Classification of Tumours of Soft Tissue and Bone (756). Non-hereditary genetic factors are also presumed to be pathogenetic in various tumour types which have consistent chromosomal translocations, although it is not known how or in what cell these rearrangements arise. Viruses associated with sarcomas include human herpes virus 8 (HHV8) in Kaposi sarcoma (434,2487), and EBV in some smooth muscle tumours in children and adults with immunosuppression, including transplant recipients and patients with HIV infection (1390,1547). Angiosarcoma complicating longstanding lymphoedema, especially after radical mastectomy (Stewart-Treves) might also be due to local immunosuppression (1995).

An association between exposure to herbicides, including dioxin, and sarcoma genesis is controversial and remains unproven. Sarcomas can arise in the field of prior therapeutic irradiation. This is a dose- and time-related phenomenon, resulting mostly in subfascial, high-grade pleomorphic sarcomas after an interval of 5 or more years. Following irradiation for carcinoma of breast, low-grade cutaneous angiosarcomas have been described after an interval as short as 18 months (1772).

Clinical features
Benign and malignant tumours present as usually painless masses, with varying growth rate. Cutaneous lesions form a plaque or elevated nodule that can ulcerate when malignant. Large (>5 cm) superficial lesions, and all subfascial or deep-seated tumours, should be referred to a specialist multidisciplinary centre before surgery and preferably before biopsy (180).

Pathology
In general, malignant soft tissue neoplasms are characterized by nuclear pleomorphism, mitotic activity including abnormal forms, necrosis and vascular invasion. Some benign tumours, however, can show one or more of these features. Examples include nuclear atypia in cutaneous pleomorphic fibroma and atypical benign fibrous histiocytoma (which can also display necrosis), and frequent mitoses in nodular fasciitis. Detailed diagnostic criteria are provided for each subtype.

Diagnostic procedures
Investigation includes clinical assessment of size and depth of tumour, the use of imaging modalities, and biopsy.

Imaging
Imaging is of value for assessing the extent of a primary tumour and its relationship to normal structures, and for revealing metastases. Both computerized tomography (CT) and magnetic resonance imaging (MRI) are used. CT is particularly useful for tumours in body cavities, and for detecting pulmonary metastases. MRI can demonstrate intratumoural heterogeneity, including presence of solid, fatty, fibrous, haemorrhagic or necrotic tissue, and the interface between neoplastic and normal tissue including involvement of neurovascular bundles.

Biopsy
Superficial lesions smaller than 2-5 cm in diameter can be excised in their entirety. Larger ones, and all subfascial and deep-seated tumours need diagnostic sampling. For this, some practitioners prefer open incisional biopsy with an appropriately placed incision that is subsequently excised in continuity with the formal resection. Needle core biopsy, preferably using a Trucut or larger needle can provide diagnostic information for malignancy, subtype and grade, with high sensitivity and specificity in experienced hands {1021,1040}. Fine-needle aspiration cytology is used in a few centres where a large volume of cases allows accrual of sufficient experience {46}; it is not particularly sensitive for diagnosing malignancy in differentiated adipose or in sub-typing low-grade myxoid lesions, partly because the sample might not be representative.

Tumour spread and staging
The recent WHO classification of Tumours of Soft Tissue and Bone (756) recognizes three behavioural categories: 1. Benign tumours. These rarely recur locally, and those that recur do so in a non-destructive fashion and are usually cured by local excision. Exceptionally rarely, an otherwise (and histologically typical) benign tumour, such as cutaneous fibrous histiocytoma, can metasta-size.

2. Intermediate tumours are those that
are locally aggressive and/or very occasionally metastasizing. Locally aggressive tumours, such as fibromatosis, recur locally and infiltrate surrounding tissues. Rarely-metastasizing tumours are generally dermal or subcutaneous tumours which have a low (1-2%) but definite risk of metastasis, most often to regional lymph nodes but occasionally to lung. Examples are recorded for plexiform fibrohistiocytic tumour (2028) and angiomatoid fibrous histiocytoma (693).

3. Malignant tumours infiltrate and recur locally and have an appreciable risk of metastasis (exceeding 20%).

Grading
This is an attempt to predict clinical behaviour based on histological variables. Grading of a tumour should be done on material from a primary untreated neoplasm, though change (increase) of grade can be noted in recurrent or metastatic tumour. It is not applicable to all sarcomas; for example, angiosarcoma, clear cell sarcoma and epithelioid sarcoma are always considered to be of high-grade malignancy. Several grading systems have been proposed, but that of the French Cancer Centres is gaining wide usage (917). Briefly, tumours are given a score of 1, 2 or 3 depending on degree of differentiation; 1, 2 or 3 for number of mitoses per 10 hpf (<10, 11-20, or >20); and 0-2 for amount of necrosis (0, <50%, >50%). A total score count of 2 or 3 is classified as grade 1, a score count of 4 or 5 as 2, and a score of 6, 7 or 8 as grade 3.

Staging
A widely used staging system for soft tissue sarcomas is that of the International Union against Cancer (UICC) (TNM system) and American Joint Commission on Cancer (AJCC) (892,2219). Unlike for many other tumours, staging of sarcomas includes histological grading as well as tumour size and depth from surface, regional lymph node involvement and distant metastasis.

Prognosis and predictive factors
Completeness of excision (assessed by clear surgical margins in the excision specimen) is the most important factor in prevention of local recurrence (2376). Some sarcomas, notably epithelioid sarcoma, are relentlessly recurrent, even though they might not metastasize until late in the course of the disease (2238). For metastasis, general adverse factors are large tumour size and increasing depth from surface. Thus, cutaneous sarcomas have a lower risk of metastasis than those located more deeply (2001); indeed, histologically malignant leiomysarcomas confined to skin are essentially non-metastasizing tumours (1164). In some instances, histological subtype is predictive, but one of the principal factors in assessing prognosis and determining management is the histological grade. Low-grade sarcomas, however, when located in sites where complete surgical excision is difficult, such as retroperitoneum or head and neck, have a worse outcome than similar tumours in the extremities. Molecular genetic findings, especially fusion gene types, might relate to prognosis.
Haemangioma of infancy

Definition
Haemangioma of infancy (HOI) is a proliferation of benign capillaries characterized by perinatal or congenital onset, rapid proliferation in the first year, followed by spontaneous regression. Strong expression of GLUT1 is distinctive.

ICD-O code 9131/0

Synonyms
Infantile haemangioma, juvenile haemangioma.

Epidemiology
HOI is the most common tumour of infancy, affecting up to 10-12% of children (1051,1119). There is a predilection for females (at least 3:1) (1663), Caucasians and premature infants (1051,1853). Presentation is exclusively in infants, although involuting lesions persist into childhood.

Etiology
The unique immunophenotypic resemblance of HOI and placental vessels suggests shared regulatory mechanisms, or possibly a common cellular origin (1723). Two recent studies have demonstrated endothelial cell clonality in HOI (295,2452), suggesting a possible role for somatic mutation (2452).

Localization
It most commonly affects the skin and subcutis of the head and neck, followed by the trunk and extremities. Visceral involvement, although rare, is most common in the liver, followed by the lung, brain, and intestine (746).

Clinical features
Nascent lesions appear as blanched macules or erythematous patches, often with central telangiectasias, typically around 2 weeks of age. Approximately 30% are congenital. Following a rapid growth phase of 3-18 months, involution occurs over several years, often leaving a fibrofatty residuum. Most develop as focal masses, although some show a diffuse, segmentally distributed pattern (2453). Although usually solitary, many affected infants have several lesions. Rare cases of “diffuse neonatal haemangiomas” have multiple small skin lesions accompanied by visceral lesions (1454).

Large facial haemangiomas may be associated with posterior fossa malformations, aortic coarctation, cardiac defects, arterial abnormalities, eye abnormalities, and aortic abnormalities, and external cephalic presentation (PHACES syndrome) (1591). Lumbo-sacral haemangiomas may be associated with spinal dysraphism, tethered cord syndrome, and other caudal abnormalities (850). MRI in the proliferative phase shows a tumoural mass with flow voids.

Macroscopy
Proliferative phase lesions show solid tan lobules, are well-defined but not encapsulated.

Histopathology
Proliferative phase lesions are cellular masses of plump endothelial cells and pericytes with abundant cytoplasm and enlarged nuclei that together form capillaries with tiny rounded lumina. Investing basement membranes are multilaminated; mast cells are numerous. The capillaries are arranged in delicately defined lobules, separated by thin fibrous septa or normal intervening tissue. Mitotic figures may be numerous; supportive arteries and veins are prominent.

During involution, endothelial cells and pericytes flatten, lumina enlarge, and mitotic figures diminish. Capillaries progressively drop out and are replaced by loose connective tissue. End-stage lesions often show isolated groups of “ghost” vessels composed of thick, acellular basement membrane rings containing apoptotic debris.

Immunohistochemistry
All stages are distinguished from other vascular tumours by their strong endothelial positivity for several antigens, including GLUT1, Lewis Y antigen, FcγRII, and IGF-II (1722,1723,1942). Basement membranes strongly express merosin (1723).

Differential diagnosis
Proliferative phase HOI must be distinguished from other cellular vascular proliferations including congenital non-progressive haemangioma, kaposiform haemangioendothelioma, tufted angioma, pyogenic granuloma, and intramuscular haemangioma. Involuting HOI may mimic vascular malformations. The characteristic GLUT1 immunoreactivity of HOI is helpful in routinely fixed specimens (1722).

Somatic genetics
HOI are generally sporadic, although autosomal dominant inheritance has been suggested in several kindreds (259). Monozygotic and dizygotic twins show no significant difference in concordance for haemangioma development (464). No cytogenetic abnormalities have been reported.

Cherry haemangioma

Definition
Cherry haemangioma (CH) is a benign, acquired, well-circumscribed aggregate of dilated capillaries and venules in the superficial dermis.

ICD-O code 9120/0

Synonyms
Campbell de Morgan spots, de Morgan spots, senile haemangioma.

Epidemiology
CH is rare before puberty, with a few lesions developing in early adulthood. Number and incidence increase through adulthood, becoming almost universally present with large numbers in some patients. Sex predilection is not a feature, with the exception of lesions that can occur in pregnancy (169).
Etiology
Age is the most common factor in the development of the majority of lesions. Eruptive cases have been reported after exposure to sulphur, mustard gas, bromide compounds and 2-butoxyethanol solvent \( (510,747,1901) \). There are two reports of outbreaks in populations, without definite causes \( (1058,2145) \). CH lesions that develop in pregnancy can involute in the puerperium and eruptive lesions have been reported in two patients with elevated prolactin levels suggesting a hormonal factor in some lesions \( (169,1924) \).

Localization
The majority of lesions are located on the trunk and upper limbs with relative sparing of the head and neck. There is no predilection for exposed skin.

Clinical features
CH begins as a barely discernible red macule that enlarges to become a slightly elevated erythematous papule 1-5 mm in diameter. It may resist blanching with pressure. Endothelial cell nuclei may be protuberant. Sheaths of hyaline multilayered basement membrane material composed of laminin, collagen IV and collagen VI surround most vessels \( (2317) \). Stromal mast cells may be increased compared to normal skin \( (938) \). The endothelial cells are fenestrated and show high levels of carbonic anhydrase \( (668) \). Ki-67 proliferating cell marker is not positive in endothelial cells of CH \( (2388) \).

Histogenesis
Ultrastructural three-dimensional studies show that CH is composed of interconnected spherical and tubular dilatations of venous capillaries and postcapillary venules in the dermal papillae \( (303) \).

Sinusoidal haemangioma
Definition
Sinusoidal haemangioma is a benign vascular neoplasm in which cavernous appearing vascular spaces occur in a well circumscribed, generally small papule or nodule. Most clinicians use the term cavernous haemangioma to refer to much larger and more poorly circumscribed lesions in infants.

ICD-O code 9120/0
Synonym Cavernous haemangioma (erroneous, in part).

Epidemiology
Most reported cases are in adult women.

Localization
The arms and torso are the most common sites \( (366) \).

Clinical features
Most sinusoidal haemangiomas are freely movable deep dermal or subcutaneous papules or small nodules. When deep, they may be colourless or bluish, but when superficial, they may be red.

Histopathology
Sinusoidal haemangiomas are round or oval and very well circumscribed dermal or subcutaneous neoplasms \( (366,1680) \). They are composed of thin walled vessels with capacious round lumena. The vessels are very closely apposed to one another (“back to back appearance”). Occasional lesions have smooth muscle in their walls. Thrombosis of vascular channels occurs in a proportion of cases. This can lead to intravascular papillary endothelial hyperplasia (a potential stimulant of angiosarcoma in a partial biopsy) and calcification may result \( (1680) \).

Hobnail haemangioma
Definition
Hobnail haemangioma (HH) \( (389,916,1584,1896,2052) \) is a benign vascular proliferation characterized by a wedge-shaped dermal proliferation of irregular vascular channels lined in its superficial portion by endothelial cells with hobnail morphology.

ICD-O code 9120/0
Synonym Targetoid haemosiderotic haemangioma

Epidemiology
HH is relatively rare and presents mainly in young to middle-aged adults with predilection for males.
of these lesions (2052). One possible origin is via trauma to lymphangiomas or angio keratomas, resulting in dispersion of endothelial cells and erythrocytes into the surrounding dermis.

Localization
Most cases occur on the lower limbs with predilection for the thigh followed by the upper extremities and the trunk. Rare lesions have been reported in the oral cavity including the tongue and gingivae.

Clinical features
Some lesions show a characteristic targetoid clinical appearance with variably pigmented ecchymotic haloes secondary to bleeding and haemosiderin deposition within the tumour (2052). Most often however, the clinical presentation is non-distinctive and the clinical differential diagnosis includes haemangioma, naevus or fibrous histiocytoma. HH is asymptomatic, usually less than 2 cm in diameter and increases in size very slowly. Patients usually describe cyclic changes (389). Multiple lesions are exceptional. Similar histological changes may occur after trauma (481).

Histopathology
The most striking low-power feature is the presence of a wedge-shaped vascular proliferation consisting of superficial, dilated and thin-walled vascular channels lined by bland endothelial cells that appear flat or have hobnail morphology. Some of the vascular channels resemble lymphatics. Focally, intraluminal small papillary projections with collagenous cores are occasionally seen. As the vascular channels descend further into the reticular dermis they gradually become smaller and disappear. Inflammation is not usually a feature. Haemorrhage and haemosiderin deposition are prominent but vary according to the stage of evolution. A Perls stain may be useful in highlighting the haemosiderin.

Immunohistochemistry
The endothelial cells in HH stain diffusely for vascular markers including CD31 and VWF (von Willebrand factor). CD34 is usually negative or very focal. A layer of alpha-smooth muscle actin pericytes surrounds some of the vascular channels. The positive staining for vascular endothelial growth factor receptor-3 (VEGFR-3) in some cases has led to the suggestion that HH displays lymphatic differentiation (1584). VEGFR-3 is however, not entirely specific for lymphatic endothelium. Staining for human herpes virus 8 is consistently negative (932).

Differential diagnosis
Kaposi sarcoma differs by the absence of dilated blood vessels lined by hobnail cells.

Prognosis
The lesion is entirely benign and there is no tendency for local recurrence.

Glomeruloid haemangioma

Definition
Glomeruloid haemangioma is a benign vascular proliferation that occurs inside ectatic blood vessels, producing a pattern reminiscent of renal glomeruli.

ICD-O code 9120/0

Epidemiology
This is a very rare vascular proliferation that occurs exclusively in patients with POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal paraproteinaemia and Skin lesions), which is associated with multicentric Castleman disease (440,2562). Multiple haemangiomas occur in 24-44% of all patients with POEMS syndrome, with most being cherry-type haemangiomas, and only some being glomeruloid haemangiomas (1301,2312,2580). The reported cases of glomeruloid haemangiomas show female predominance, with patients ranging in age from 40-68 years (440,1278,1285,1965,2083,2380, 2562).
Etiology
Glomeruloid haemangioma has so far only been found in patients with POEMS syndrome. Its development may be mediated by circulating vascular endothelial factor, which is present at high titres in the blood of most patients with POEMS syndrome (2225, 2464).

Localization
The lesions are mainly found on the trunk, face and proximal limb, and exceptionally also in the fingers and deep soft tissues (440, 1278, 1285, 1965, 2380, 2562).

Clinical features
The lesions manifest as multiple purplish-red papules or nodules, ranging in size from a few to 15 mm (1278, 1285, 1965, 2380, 2562). They occur in patients already known to have POEMS syndrome, or as an early phenomenon before the full-blown syndrome develops (1278, 1285, 1965, 2083, 2380, 2562).

Histopathology
Glomeruloid haemangioma is mainly centred in the upper and mid dermis. It is characterized by tufts of proliferated, coiled capillaries projecting inside thin-walled ectatic blood vessels, mimicking renal glomeruli. The “sinusoidal” endothelial cells that line the ectatic vascular spaces and the surface the vascular tufts possess dark round nuclei. These cells also show cleft-like extensions into the cores of the vascular tufts. The capillary loops within the tufts are lined by plump endothelium with slightly larger and paler nuclei, and supported by pericytes. Scattered “interstitial” cells that contain PAS-positive eosinophilic globules are found between the capillary loops, but similar cytoplasmic globules can also be seen in some endothelial cells.

Immunohistochemistry
On immunohistochemical staining, the endothelial cells of the capillary loops stain for CD31 and CD34, and they are well supported by actin-positive pericytes. The sinusoidal endothelial cells covering the tufts are positive for CD31 but not CD34, while those lining the ectatic vascular spaces are strongly CD31 positive but weakly CD34 positive. The eosinophilic globules probably represent immunoglobulin. The cells that contain these globules represent a mixture of histiocytes (CD68+) and endothelial cells (CD31+).

Precursor lesions
Progression from cellular immature, non-specific, vascular proliferation with slit-like canals reminiscent of tufted angioma to classical glomeruloid haemangioma has been reported (2562). In addition, cherry-type haemangiomas with miniature glomeruloid structures formation can coexist with glomeruloid haemangiomas in patients with POEMS syndrome (440). Thus these might represent precursor lesions of glomeruloid haemangioma.

Histogenesis
The currently favoured view is that glomeruloid haemangioma is a reactive vascular proliferation, perhaps representing a distinctive form of reactive angioendotheliomatosis.

Prognosis and predictive factors
Glomeruloid haemangioma per se is a totally innocuous lesion. The outcome of the patients depends on the underlying POEMS syndrome.

Microvenular haemangioma

Definition
Microvenular haemangioma is an acquired, slowly growing asymptomatic lesion with an angiomatous appearance (1080).

ICD-O code
9120/0

Etiology
A histogenetic relationship between microvenular haemangioma and hormonal factors such as pregnancy and hormonal contraceptives has been postulated (144, 2065), but this feature has not been corroborated by other authors. An example of microvenular haemangioma has developed in a patient with Wiskott-Aldrich syndrome (1939). Haemangiomas identical to microvenular haemangioma can be seen in patients with POEMS syndrome (25).

Localization
It most commonly affects the upper limbs, particularly the forearms.

**Fig. 5.3 Glomeruloid haemangioma.**

A The dermis shows a vascular proliferation occurring exclusively within thin-walled ectatic vascular spaces, producing a glomerulus-like appearance. B The vascular proliferation consists of aggregates of capillaries projecting as a broad tuft into a vascular space. The endothelial cells that line the vascular space and surface of the tuft have dark-staining nuclei (“sinusoidal endothelium”), while those that line the capillaries have plumper and paler nuclei. *Interstitial* cells containing eosinophilic hyaline globules are also seen.
However, lesions on the trunk, face and lower limbs have also been recorded (65,1061).

**Clinical features**
Microvenular haemangiomas appear as sharply circumscribed, bright red, solitary lesions varying in size from 0.5-2 cm.

**Histopathology**
Microvenular haemangioma appears as a poorly circumscribed proliferation of irregularly branched, round to oval, thin-walled blood vessels lined by a single layer of endothelial cells. They involve the entire reticular dermis and a variable degree of dermal sclerosis is present in the stroma. The lumina of the neoplastic blood vessels are inconspicuous and often collapsed with only a few erythrocytes within them.

The main differential diagnosis is with Kaposi sarcoma in the patch stage. Kaposi sarcoma shows irregular anastomosing vascular spaces, newly formed ectatic vascular channels surrounding pre-existing normal blood vessels and adnexa (promontory sign), plasma cells, hyaline (eosinophilic) globules, and small interstitial fascicles of spindle cells. All of these features are absent in microvenular haemangioma.

**Immunohistochemistry**
Immunohistochemically, the cells lining the lumina show positivity for factor VIII-related antigen and Ulex europaeus I lectin (144,1080,2065) which qualifies them as endothelial cells. Some smooth muscle actin positive perithelial cells have been also described surrounding this vascular space (65,1061).

**Prognosis**
Microvenular haemangioma is a benign neoplasm and it is cured by simple excision.

**Angiolympoid hyperplasia with eosinophilia**

**Definition**
Angiolympoid hyperplasia with eosinophilia (ALHE) is a benign skin or subcutaneous tumour that is a circumscribed combined proliferation of immature blood vessels and chronic inflammatory infiltrate usually containing eosinophils. Endothelial cells have a distinctive epithelioid or histiocytoid appearance with ample eosinophilic cytoplasm.

**Synonyms**
Epithelioid haemangioma, cutaneous histiocytoid angioma, pseudo- or atypical pyogenic granuloma, inflammatory angiomatous nodule, intravenous atypical vascular proliferation, nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis (201,1154, 1967,1968,2381).

**Epidemiology**
ALHE was originally described as a lesion commonly found in young women on the head and neck (1011). Recent reviews show a wide age range peaking at 20-50 years without female predominance (738,1753). There is no predilection for Asian populations.

**Etiology**
Reactive vascular proliferation and inflammation (2441) in a traumatized vascular structure is a postulated cause of some ALHE lesions. History of antecedent trauma, histologic evidence of
adjacent vascular damage \(738,2400\) and pre-existing arteriovenous malformation \(1754\) are found in some cases. Although earlier reported, HHV-8 has not been consistently found in ALHE \(1130,1241\).

**Localization**
ALHE most commonly occurs on the head and neck with a predilection for the forehead, scalp and skin around the ear \(738,1011,1753\). Occurrence on distal extremities and digits is not uncommon \(97\). Multiple other reported sites include trunk, breast \(1676\), oral mucosa \(1512,1530,1776\), orbital tissues \(145,1513\), vulva \(37,2125\) and penis \(2240\).

**Clinical features**
ALHE lesions are small red or violaceous papules or plaques with an average size of 1 cm, measuring up to 10 cm. When symptomatic they can be pulsatile, painful and pruritic with scale crust \(1011,1753\). When multiple they are usually grouped or zosteriform \(647\) and may coalesce. In contrast to Kimura disease, lymphadenopathy, eosinophilia, asthma and proteinuria are uncommon and serum IgE is usually normal \(97,441\).

**Histopathology**
The lobulated, circumscribed dermal or subcutaneous proliferation has a combined vascular and inflammatory component. Sometimes an origin from a medium-sized vessel, usually a vein, is seen. There are arborizing small blood vessels that may surround a larger vascular structure. The vessel walls have smooth muscle cells or pericytes and contain mucin. The endothelial cells have distinct abundant eosinophilic (epithelioid) cytoplasms that can be vacuolated. They protrude into and can occlude vascular lumina or form solid sheets that may mimic angiosarcoma \(2582\). Their nuclei have open chromatin, often with a central nucleolus and may protrude into lumina with occasional mitoses. Multinucleate cells that are endothelial sprouts or histiocyte-like cells can be present \(2020\). The density of the inflammatory component between vessels is variable with a prominence of lymphocytes and eosinophils. Plasma cells, mast cells and lymphoid follicles with reactive germinal centres can be present. Older lesions typically become more fibrotic, less inflammatory and their vascular nature becomes less conspicuous.

**Immunoprofile**
The endothelial cells are positive for CD31, CD34, VWF (VIIIrAg) and are keratin negative. The proliferative index of the endothelial cells has been reported as 5% using Ki-67 with negative staining for Cyclin D1 and bcl-2. This may support a reactive rather than neoplastic endothelial proliferation \(97\). Lymphocytes are a mixture of T- and B-cells. There is no light chain restriction \(97,1753\). One series has shown T-cell clonality in ALHE that may define a subgroup of lesions with a higher incidence of recurrences \(1241\).

**Differential diagnosis**
Kimura disease is a distinct clinicopathological entity, characterized by a more prominent lymphoid proliferation and less prominent vascular component with almost complete absence of epithelioid endothelial cells.

**Prognosis and predictive factors**
The lesions tend to persist if not completely excised and only rarely will they spontaneously regress. Local recurrence can occur and may be related to persistence of an underlying arteriovenous fistula that is not completely excised \(97,1753,1754\).

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**Spindle cell haemangioma**

**Definition**
Spindle cell haemangioma is a benign...
vascular tumour composed of an intimate admixture of cavernous blood vessels and Kaposi sarcoma-like spindle cell vascular zones.

ICD-O code 9136/0

Synonym Spindle cell haemangioendothelioma (1807,2488)

Epidemiology The tumour is uncommon, and mainly affects children and young adults. Those who present late in adulthood usually have long-standing tumours (270,1807). There is no sex predilection.

Etiology In a small proportion of cases, spindle cell haemangioma develops in the setting of multiple enchondromas (Maffucci syndrome), Klippel-Trenaunay syndrome, venous malformation, early onset varicose veins, or congenital lymphoedema (709,754,1807). The onset in young patients and frequent finding of abnormal vessels around the lesion suggest that an underlying vascular malformation may predispose to the development of spindle cell haemangioma (754).

Localization They occur on the distal extremities and less commonly on the proximal limb, trunk, head and neck (1807). Exceptionally, it has been reported in the spleen (709).

Clinical features The tumour usually presents as a superficial, slow-growing, painless, solitary purplish mass, or multiple nodules within an anatomical region (1807). Rare examples may be painful (1784). The lesion is a discrete red-brown nodule that ranges in size from a few mm to over 10 cm, but most are smaller than 2 cm.

Histopathology Spindle cell haemangiomas are mostly found in the dermis and subcutis, and occasionally in the deep soft tissues. The tumour is often well-circumscribed but non-encapsulated. It is characterized by intricate blending of cavernous and solid spindle cell zones. The cavernous blood vessels are empty or filled with blood, and may contain organizing thrombi or phleboliths. In the spindle cell regions, short fascicles of spindle cells are interspersed with ramifying narrow vascular spaces. The spindle cells possess uniform, elongated, dark nuclei and eosinophilic cytoplasm. There are scattered single or groups of vacuolated cells or epithelioid cells with lightly eosinophilic cytoplasm.

In about half of the cases, residual vessel walls can be found in the periphery of the lesion, indicating that the lesion is partly or entirely intravascular (754,1807). Intravascular extension of the lesion can sometimes be seen around the main lesion.

Immunohistochemistry The cells that line the vascular spaces stain for VWF (VIIIrAg), CD31 and variably for CD34. The spindle cells are negative for the various endothelial markers including CD34, and may show patchy and variable staining for actin (754,796, 1667).

Differential diagnosis Spindle cell haemangioma can be distinguished from Kaposi sarcoma by the following features: irregular-shaped, dilated and ramifying vascular spaces rather than short narrow vascular slits among the spindle cells, presence of vacuolated endothelial cells, frequent partial or complete localization within muscular blood vessels, absence of eosinophilic hyaline globules, lack of CD34 immunoreactivity in the spindle cells, and lack of association with HHV-8 (1034).

Histogenesis There are controversies on the nature of spindle cell haemangioma, with theories ranging from neoplastic, malformative to hamartomatous (754,1100,1807). The lesion itself comprises heterogeneous cellular populations, including endothelial cells, pericyte-like cells, fibroblasts, smooth muscle cells and primitive mesenchymal cells.

Somatic genetics There are no molecular data on spindle cell haemangioma; one studied case shows a normal karyotype (754). The lesions are diploid on flow cytometric analysis (796,1035).

Prognosis and predictive factors Recurrence after local excision occurs in 50-60% of cases, and often results from new lesions developing within the same anatomical region due to intravascular extension. However, there is no metastatic potential.

Tufted angioma

Definition Tufted angioma is an unusual, acquired, benign vascular neoplasm characterized by slow, indolent growth (1153,1475).

ICD-O code 9161/0

Synonyms Tufted haemangioma, progressive capillary haemangioma, angioblastoma of Nakagawa.

Epidemiology Tufted angioma most commonly affects children and young adults, but both congenital and very late onset cases have been described (995,1264).

Histopathology Another example of a tufted angioma present in the dermis and subcutaneous tissue.
Localisation
Tufted angioma favours the shoulders, upper chest, back, and neck (1747), although examples of these lesions have also been reported on the oral mucosa, extremities and head (1289,2458).

Clinical features
The most common forms of presentation are enlarging erythematous, brown macules or plaques with an angiomatous appearance. In other instances the lesions resemble granulomas or a connective tissue naevus. Pain and hyperhidrosis have been described (216,2291). Raised papules or nodules resembling pyogenic granulomas are sometimes seen within the lesion and occasionally they adopt a linear arrangement (1765). In some cases the patients present with sclerosing plaques (412). Tufted angiomas have been associated with vascular malformations including naevus flammeus (1267,1601), pregnancy (1272), non-regressing lipodystrophy centrifugalis abdominalis (1032), and liver transplant (482). In some cases of Kasabach-Merritt syndrome the underlying lesion is a tufted angioma (691,692, 2136). In most cases the growth is halted after some years, and in some cases there is a slight tendency towards spontaneous regression (1131). Tufted angioma grows slowly and insidiously, and may eventually come to cover large areas of the body.

Histopathology
There are multiple individual vascular lobules within the dermis and subcutaneous fat. These aggregations are more prominent in the middle and lower part of the dermis. Each lobule is composed of aggregates of endothelial cells that whorl concentrically around a pre-existing vascular plexus. Some lobules bulge into the walls of dilated thin-walled vascular structures, creating a slit-like or semi-lunar appearance of vessels. This peculiar shape in addition to the angiocentricity of the vascular structures prompted the name “tufted angioma.” Small capillary lumina are identified within the aggregations of endothelial cells. Unusual histopathologic findings in tufted angioma include a mucinous stroma, abundant sweat glands (137), an intravenous location (795) of the lesion and a proliferation of lymphatic-like channels.

Immunohistochemistry
Cells in the capillary tufts are weakly positive or negative for VWF (VIIIrAg). They exhibit strong positivity for CD31, CD34 and alpha-smooth muscle actin (1156, 1709). The cells that show reactivity for smooth muscle actin, most likely represent pericytes.

Electron microscopy
Ultrastuctural studies have shown characteristic crystalloid inclusions within endothelial cells in addition to Weibel-Palade bodies (1709).

Genetics
Most cases are sporadic, although a family with several members affected by tufted angioma has been reported (993). In this particular family the mode of transmission was autosomal dominant.

Prognosis
Tufted angioma showing spontaneous regression is a rare event. Although benign, symptomatic lesions need to be treated (1131,1709,1948).

Bacillary angiomatosis
Definition
Bacillary angiomatosis is a reactive vascular proliferation caused by infection with bacteria of the genus Bartonella, most commonly B. henselae and B. quintana (507,855,1383,1845,2492).

Synonyms
Disseminated pyogenic granulomas (not generally accepted), epithelioid angiomatosis.

Epidemiology
Bacillary angiomatosis most commonly occurs in immunosuppressed patients although there have been a few reports in apparently immunocompetent patients, both adults and children (504,507,1233,1383,1613,1793,1845,2111,2206,2325). Bacillary angiomatosis has most frequently been seen in HIV/AIDS patients.

Localization
Cutaneous involvement may occur at any site and less commonly lesions may involve mucosal surfaces and deeper soft tissue such as muscle, bone, lymph node and liver (peliosis hepatis) (442,507,1383,1845,2085).

Clinical features
The lesions present as multiple reddish to red-brown cutaneous nodules and occasionally as subcutaneous nodules. In immunocompetent patients there may be fewer nodules (507,1383,1845).

Histopathology
Sections show a lobular proliferation of well-formed vessels with plump occasionally epithelioid endothelial cells. There is an oedematous to fibrous stroma with a variable infiltrate of neutrophils with nuclear dust, macrophages and ill-defined pale basophilic granular material (representing the bacteria). Diagnosis is made by identifying the characteristic coccobacillary organisms with a Warthin-Starry or Giemsa stain (507, 1383,1845).

Differential diagnosis
Pyogenic granuloma lacks the characteristic basophilic granular material and the dispersed pattern of neutrophils seen in bacillary angiomatosis. Histologically identical lesions can be seen in verruca peruana (verruca peruana).
Prognosis and predictive factors
The infection may be cleared by antibiotics with resolution of the lesions. The overall prognosis depends upon the immune status of the patient and sites of involvement (507,1383,1845).

Reactive angioendotheliomatosis

Definition
Reactive angioendotheliomatosis (RA) is a relatively rare condition associated with diverse systemic diseases, usually confined to the skin and characterized by a multifocal dermal proliferation of capillaries (1559,2513).

Synonym
Diffuse dermal angiomatosis. The so-called malignant angioendotheliomatosis represents a form of intravascular lymphoma not related to reactive angioendotheliomatosis (2512).

Epidemiology
Presentation is mainly in adults with no sex predilection. Occurrence in children is exceptional (304).

Localization
There is a predilection for the trunk and limbs.

Clinical features
Clinical presentation is variable and consists of fairly widespread erythematous macules, papules, nodules and plaques (1559,2513). Purpura is a frequent finding. Ulceration is very rare. Many systemic illnesses are related to the development of RA and it can be said that this condition often represents a marker of systemic disease. Patients affected with RA not uncommonly are immunosuppressed as a result of transplantation. Many conditions have been associated with reactive angioendotheliomatosis including valvular cardiac disease, alcoholic cirrhosis, rheumatoid arthritis, polymyalgia rheumatica, cryoglobulinaemia, the antiphospholipid syndrome, and sarcoidosis (551,1385,1559,2178,2341,2361). A more localized variant may be seen in some patients and it is usually associated with peripheral vascular atherosclerosis or iatrogenic arteriovenous fistulas (1266,1276,1918).

Histopathology
Histologically, the dermis and rarely the superficial subcutaneous tissue show numerous clusters of closely packed capillaries. Many of these capillaries proliferate within pre-existing blood vessels. Cytological atypia is mild or absent but endothelial cells are often prominent and may show focal epithelioid cell change. A layer of pericytes surrounds the newly formed small vascular channels. Extravasation of red blood cells tends to be prominent. PAS positive microthrombi are numerous in cases associated with cryoglobulinaemia. Dermal changes resembling fasciitis have also been described.

Differential diagnosis
Distinction from Kaposi sarcoma is easy as in RA there is no proliferation of individual irregular lymphatic-like channels around pre-existing normal blood vessels, proliferating vascular channels are surrounded by a layer of pericytes and inflammatory cells are very rare or absent. Tufted angioma may be distinguished from RA by the typical cannonball appearance at scanning magnification and the presence of slit-like crescent shaped lymphatics around individual tufts in the former. An unusual entity characterized by the presence of aggregates of histiocytes within vascular lumina and described as intravascular histiocytosis has been recently described and may closely mimic reactive angioendotheliomatosis (1935). Distinction from the later may be difficult and in difficult cases immunohistochemistry is useful in demonstrating the histiocytic nature of the intravascular cells.

Prognosis and predictive factors
RA tends to be self-limiting in the majority of cases with complete spontaneous resolution over weeks or months.

Fig. 5.10 Bacillary angiomatosis. A Low power view of a skin lesion of bacillary angiomatosis shows dome shaped expansion of the upper dermis due to a proliferation of small well formed vessels. B High power view showing the plump endothelial cells lining the vessels. C A Warthin-Starry stain shows the small coccobacillary organisms.
**Verrucous haemangioma**

**Definition**
Verrucous haemangioma (VH) is an uncommon variant of haemangioma with capillary or cavernous features (444, 2489). It is evident at birth or in early childhood and enlarges and becomes hyperkeratotic in later life.

**Synonyms**
Haemangioma unilateralis naeviforme, unilateral verrucous haemangioma, angiokeratoma circumscriptum naeviforme, naevus vascularis unius lateralis, keratotic haemangioma, naevus angiokeratoticus, naevus keratoangiomaticus (363).

**Epidemiology**
VH is usually apparent at birth or in the first few years of life (1102). The condition is rare, and there is no known gender predilection.

**Localization**
VH is almost always a unilateral isolated condition, with most cases affecting the leg. Less commonly, it presents on the arm. It is not common on the trunk, but when present on the back in association with underlying spinal malformation, it is a component of Cobb syndrome.

**Clinical features**
The condition usually presents with lesions that are clustered, discrete to nearly confluent, bluish-red, well demarcated, soft and compressible (363, 444, 1102). The lesions that comprise these clusters may coalesce to form large lesions that cover broad areas over time. Satellite lesions are typical. The condition may show linear or serpiginous distribution. Lesions become hyperkeratotic over time and show a brown to bluish-black appearance. Hyperkeratosis may be so pronounced as to appear verrucous; consequently, the lesion may be mistaken clinically for a wart or keratosis (2560). Size usually allows distinction from the later two, as verrucous haemangioma tends to be large.

**Histopathology**
Within the superficial and deep dermis and sometimes the subcutis there are dilated capillaries and venules. Vessels tend to be cavernous in the upper dermis, few in numbers in the deep dermis, and capillary-like in the subcutis. A pseudo-infiltrating pattern may be seen in the subcutis, but close inspection reveals an overall lobulated pattern (444). There may be thrombosis with secondary papillary endothelial hyperplasia. The vessels are lined by a single layer of endothelial cells without evidence of endothelial proliferation. Inflammatory cells, haemosiderin and fibrosis may be associated. Older lesions show prominent acanthosis, hyperkeratosis with crust and papillomatosis. Ulceration is sometimes present.

**Differential diagnosis**
Angiokeratoma may also show verrucous epidermal hyperplasia. Verrucous haemangioma differs from angiokeratoma by its large size, involvement of deep vasculature and the presence of vessels that usually vary significantly in size. Angiokeratomas also show a hereditary basis in some cases, are often multiple and show a predilection for the lower trunk, thigh and external genitalia (444).

**Prognosis and predictive factors**
VH has a propensity to recur locally (2489). The condition progresses over time, and superficial therapy has been reported to exacerbate spread (2560). This may be due, in large part, to the fact that size of the lesion is usually underestimated clinically (444). Recurrence may also be seen in skin grafts.

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**Fig. 5.11** Verrucous haemangioma. **A** A large, irregularly outlined, hyperkeratotic lesion is typical of verrucous haemangioma. **B** This low magnification view of verrucous haemangioma exhibits a superficial and deep proliferation of variously sized blood vessels.
**Pyogenic granuloma**

**Definition**

Pyogenic granuloma (PG) are rapidly growing, mostly exophytic lesions which may ulcerate.

**Synonym**

Lobular capillary haemangioma

**Epidemiology**

An epidemiologic study of 325 cases, (959) showed that 86% of the lesions were cutaneous, while only 12% of the cases affected mucosa. Overall, male patients outnumbered female patients. Pyogenic granuloma is especially common in children and young adults and the peak incidence is around the second decade of life.

**Etiology**

Most authors consider PG to be a hyperplastic rather than a neoplastic process (598,1615). Most lesions develop at sites of superficial trauma; in some cases lesions of PG are associated with endocrine alterations or medication and usually regress upon cessation of the stimuli.

**Localization**

PG preferentially affects the gingiva, lips, mucosa of the nose, fingers, and face (1247,1619), but examples of pyogenic granuloma have been described in all parts of the skin and mucous membranes including vulva, scrotum, penis, and glans penis (10,929,1477,2360).

**Clinical features**

PG presents typically as a papule or polyp with a glistening surface, which bleeds easily. Pyogenic granuloma usually develops at the site of a pre-existing injury. The lesions evolve rapidly over a period of weeks to a maximum size, then shrink and become replaced by fibrous tissue, which disappears within a few months. Epulis gravidarum a gingival lesion that develops during pregnancy, is identical to pyogenic granuloma (1669). Occasionally, pyogenic granuloma develop within a pre-existing lesion such as a naevus flammeus (1394) or in a spider angioma (1748). Multiple lesions tend to be localized (1787,2309) but they can also extend in an eruptive and disseminated fashion (2533). With few exceptions, multiple recurrent lesions are more common in adolescents and young adults, and they usually occur after attempts of electrodesiccation or surgical removal of the primary single lesion. Multiple lesions may also occur after removal of other lesions such as melanocytic neoplasms (621) or in burns (435). Multiple lesions most commonly affect the trunk, especially the interescapular region. In some cases, eruptive widespread lesions of pyogenic granuloma are a paraneoplastic manifestation (1800). Rare variants of pyogenic granuloma include the subcutaneous (1777) and intravenous (540) forms.

**Histopathology**

Early lesions of pyogenic granuloma are identical to granulation tissue, containing numerous capillaries and venules disposed radially to the skin surface, which is often eroded and covered with scabs. The stroma is oedematous and contains mixed inflammatory infiltrates with lymphocytes, histiocytes, plasma cells, neutrophils and an increased number of mast cells. Fully developed lesions of pyogenic granuloma are polyloid and show a lobular pattern with fibrous septa intersecting the lesion; hence the name lobular capillary haemangioma used by some authors for lesions at this stage. Each lobule is composed of aggregations of capillaries and venules lined by plump endothelial cells. At this stage most lesions have entirely re-epithelialized, and the epidermis forms collarettes of hyperplastic adnexal epithelium at the periphery, partially embracing the lesion; inflammatory infiltrates are sparse and the oedema of the stroma has disappeared. In the late stages of pyogenic granuloma there is a steady increase in the amount of fibrous tissue, so that the fibrotic struts widen, the lobules of capillaries become smaller and, with time, pyogenic granuloma evolves into a fibroma. When the specimen is deep enough, a small feeding artery and one or more veins may be seen ascending from the subcutaneous fat throughout the reticular dermis to directly enter the base of a pyogenic granuloma. The histopathological findings are the same in all variants of pyogenic granuloma. Uncommon histopathological features in lesions of pyogenic granuloma include intravascular papillary endothelial hyperplasia (1103) and extravascular haematopoiesis (1986). When the lesions of PG recur they may show some atypical features which in some cases resemble an angiosarcoma especially in the deeper areas of the lesion. When lesions of PG develop within a vein, they are usually attached to the wall of the vein by a stalk and the lobular pattern is less prominent than in their extravascular counterparts.

**Immunohistochemistry**

PG lesions express factor VIII related antigen positivity in the endothelial cells lining large vessels, but are negative in the cellular areas (346), whereas Ulex europaeus I lectin binds to the endothelial cells in both large vessels and cellular aggregates (1606). There is also expression of inducible nitric oxide synthase (2169), increased expression of vascular endothelial growth factor (298), low apoptotic rate expression of Bax/Bcl-2 proteins (1682), and strong expression of phosphorylated mitogen activated protein kinase (79) in lesions of pyogenic granuloma.

PCR investigations for human papillomavirus (1615) and human herpes virus type 8 (HHV8) (598) have yielded negative results.

**Prognosis and predictive factors.**

Lesions of PG are benign and easily removed by electrodesiccation and curettage; however lesions may recur, especially in those cases in which the proliferating vessels extend deep within the reticular dermis.

**Cavernous haemangioma**

Until a few years ago, the term “cavernous haemangiomas” was used to designate venous malformations. These lesions were also erroneously considered to be neoplasms, when in reality they are vascular malformations. They consist of slow-flowing, haemodynamically inactive vascular malformations, which are present at birth and slowly but progressively worsen throughout the lifetime of the patient. In some cases the lesions form a continuum of localized venous malformations, which include blue capillary spongy blebs, “cavernous” lesions (in which the venous lacunae are connected to the venous circulation by capillaries), localized saccular anomalies (connected by veins to the venous circulation) and diffuse venous edematos. Many of the apparently localized and
superficial venous lesions tend to coexist with venous ectasias and deep vein anomalies.

**Angiokeratomas**

**Definition**
Angiokeratomas are acquired vascular lesions that result from the ectatic dilatation of pre-existing vessels in the papillary dermis, accompanied by hyperkeratotic epidermis (1101). Four clinical variants of angiokeratomas have been recognized, these are: solitary, angiokeratoma corporis diffusum, Mibelli and Fordyce.

**Epidemiology**
Solitary angiokeratomas affect mainly young adults. Angiokeratoma of Fordyce affects elderly people (34), however, there are examples of congenital cases (768). Mibelli angiokeratomas usually appear in childhood or adolescence and they are more common in females (986). Angiokeratomas of Fabry disease usually appear shortly before puberty and as an X-linked disease, they exclusively affect males; females may be asymptomatic carriers. Fabry disease is a rare error of the metabolism that results in a deficiency of the lysosomal enzyme hydrolase alpha-galactosidase A. It is transmitted as an X-linked recessive trait, the gene responsible for the coding of alpha-galactosidase A has been localized to the middle of the long arm of the X chromosome (250,770).

**Etiology**
Solitary angiokeratomas are thought to be the result of injury, trauma, or chronic irritation to the wall of a venule in the papillary dermis.

Fordyce angiokeratomas are usually associated with varicocoele, inguinal hernia and thrombophlebitis (1788). The lesions may develop after surgical injuries to the genital veins (857), and there have been cases of angiokeratomas involving the glans penis mucosa of young patients developing after circumcision surgery (249). Similar lesions have been described in the vulva of young females (403,857). These lesions are thought to be the result of increased venous pressure that occurs during pregnancy or develops secondarily to the use of contraceptive pills.

Mibelli angiokeratoma is a condition that is inherited in an autosomal dominant fashion. Angiokeratoma corporis diffusum is the most unusual variant of all the angiokeratomas. It represents a cutaneous manifestation of a group of hereditary enzymatic disorders, but there is also an idiopathic form that presents with no other associated anomalies. Fabry disease is the disease most commonly associated with angiokeratoma corporis diffusum.

**Localization**
Solitary angiokeratomas may affect any anatomic site, including the oral cavity, although the lower limbs are the most frequent location (1101). Fordyce angiokeratomas are most common in the scrotum and vulva. Mibelli angiokeratomas usually affect the dorsum of the fingers, toes and interdigital spaces. Lesions of angiokeratoma corporis diffusum in Fabry disease affect the lower part of the abdomen, genitalia, buttocks, and thighs in a bathing-trunk distribution.

**Clinical features**
Although their biologic significance varies greatly, angiokeratomas range from lesions that have very little clinical repercussion to widespread eruptions that are a manifestation of potentially fatal, systemic, metabolic diseases. Solitary angiokeratomas consist of small, warty, black, well-circumscribed papules. Sometimes solitary angiokeratomas develop thrombosis and recanalization with the development of secondary intravascular papillary clinically endothelial hyperplasia. Due to their colour, these lesions may be clinically confused with malignant melanoma (857). Fordyce angiokeratoma is characterized by the presence of multiple purple to dark red papules, measuring 2-4 mm in diameter. In Mibelli angiokeratoma, the lesions consist of several dark papules with a slightly hyperkeratotic surface, and may be associated with acrocyanosis and chilblains. In rare instances, ulceration of the fingertips may appear as a complication of Mibelli angiokeratoma (592). Lesions of angiokeratoma corporis diffusum are small punctate dark red papules, some of them less than 1 mm in diameter. A frequent and asymptomatic finding is the so-called cornea verticillata, which is a superficial corneal dystrophy. This finding is of diagnostic importance for the detection of mild cases and female carriers. Other cutaneous manifestations include dry skin, anhidrosis, hyperthermic crises (1198), and acroparesthesiae secondary to capillary changes in the nail matrix (1132). In rare instances patients with Fabry disease may also present with concurrent Klippel-Trenaunay-Weber syndrome (821). Patients with Fabry disease who are devoid of cutaneous lesions have been reported (497). Angiokeratoma corporis diffusum is not exclusive to Fabry disease and has also been described in association with other rare inherited lysosomal storage diseases. By the same token, rare cases of angiokeratoma corporis diffusum have been described in patients without metabolic anomalies (565,1518). In some of these patients the angiokeratomas were multiple and presented in a zosteriform distribution.

**Histopathology**
All variants of angiokeratomas are identical under a conventional microscope. Common features of all angiokeratomas include the presence of dilated thin-walled blood vessels, lined by a layer of endothelial cells, in the papillary dermis and a variable degree of hyperkeratosis (1101). Occasionally, angiokeratomas may be seen overlying deep vascular malformations (1323). Hyperkeratosis is usually absent in Fordyce angiokeratomas and in angiokeratoma corporis diffusum (Fabry disease). In patients with Fabry disease there is vacuolization of the cytoplasm of the endothelial cells of the arterioles and smooth muscle cells of the arrector pili. The presence of these vacuoles may be a clue to the specific diagnosis in sections stained with haematoxylin and eosin. However, in most cases the amount of glycolipid in the skin is small making it extremely difficult, if not impossible to identify them, in routinely prepared sections. Special stains such as Sudan black B and PAS highlight the presence of glycolipid deposits within the vacuoles in patients with Fabry disease and related disorders. The lipid material is double refractile, which can be demonstrated by means of polaroscopic examination of unfixed, or formalin fixed frozen sections. Deposits of glycolipids in Fabry disease are not restricted to the lesions of angiokeratoma, but may also be seen in skin that appears to be normal.
Electron microscopy
Ultrastructural studies in angiokeratomas have demonstrated quantitative alterations of cytoplasmic organelles within the endothelial cells (833). Electron microscopy examination of the skin in Fabry disease show large electron dense lipid deposits in endothelial cells, pericytes, fibroblasts, arrector pili muscles and in secretory, ductal, and myoepithelial cells of the eccrine glands (1683). These deposits show a characteristic lamellar structure (1366,2438), not seen in other types of angiokeratomas or in lesions of angiokeratoma corporis diffusum with no enzymatic anomalies. Other ultrastructural findings in patients with Fabry disease consist of intersecting short crescent shaped, tightly packed membranes in the endothelial cells of the small cutaneous blood vessels (679) and cytoplasmic vacuoles in the epithelial cells of the eccrine glands (1094).

Arteriovenous haemangioma

Definition
Arteriovenous haemangiomas are benign, asymptomatic vascular proliferations. They are not associated with significant arterio-venous shunting.

ICD-O code 9123/0

Synonyms
Cirsoid aneurysm, acral arteriovenous tumour (384,385,528,1811).

Epidemiology
It occurs mainly in middle-aged adults, with no sex predilection.

Localization
Arteriovenous haemangioma is a neoplasm mainly affecting facial skin. Intraoral and vulvar examples have been also described (1318,1376,1698,1972).

Clinical features
Arteriovenous haemangioma presents as a red, purple, or skin coloured asymptomatic papule measuring 0.5-1.0 cm. Usually the lesions are solitary, although multiple examples have been cited. When the lesions are multiple they tend to cluster. Occasionally, they are associated with other abnormalities including epidermal naevus syndrome, vascular hamartomas and malformations (372).

Several examples of multiple arteriovenous haemangiomas have been described in patients with chronic liver disease (47).

Macroscopy
Grossly, lesions of arteriovenous haemangioma present as raised papules and on sectioning there is an admixture of white and red to brown areas, which represent the walls of the thick blood vessels containing blood.

Histopathology
Arteriovenous haemangioma is a well-circumscribed vascular proliferation that involves the upper and mid reticular dermis. The neoplasm is composed mainly of thick-walled muscle-containing blood vessels, lined by a single layer of endothelial cells. Intermingled with the thick-walled blood vessels are thin-walled dilated blood vessels and variable amounts of mucin. Although the thick-walled blood vessels resemble arteries, they lack a well-formed elastic internal membrane, and most likely represent ectatic veins (1318). In about one-fourth of the studied cases it is possible to identify both the arteriovenous shunts and the spiralled ascending small muscular artery (“feeder” vessel) with serial sections (834). The lesions recently described as symplastic haemangioma probably represent ancient arteriovenous haemangiomas with atypical cells due to degenerative changes that occur in long-standing lesions (1351).

Histogenesis
The precise nature of arteriovenous haemangioma is uncertain. Initially it was considered to be a multicentric hamartoma of the sub-papillary vascular plexus with one or more arteriovenous anastomoses (834). Other authors have suggested that a hamartoma of the Sucquet-Hoyer canal of the glomus body is the cause of this lesion. The latter interpretation, however, is unlikely because glomus cells are usually absent in arteriovenous haemangioma, and to date, they have been identified in only one example of all the reported cases (1318).

Prognosis
Arteriovenous haemangioma is a benign lesion and local excision suffices.

Cutaneous angiosarcoma

Definition
Angiosarcoma is a malignant neoplasm of endothelial cells. Differentiation between lymphangiosarcoma and sarcomas with blood vascular differentiation appears problematic at the current time.
ICD-O code 9120/3

Synonyms
Lymphangiosarcoma, haemangiosarcoma.

Epidemiology
There are low-grade forms of angiosarcoma that can occur outside the circumscribed clinical settings detailed herein. Almost all high-grade angiosarcomas are in one of the following settings: the head and neck of predominantly male elderly patients (the most common setting) (1046), the chest of patients who have undergone mastectomy for breast cancer (Stewart-Treves syndrome) (2269), lymphoedema (congenital or acquired), or post-irradiation (2271).

Localization
Most of the epidemiologic settings also define the sites of disease.

Clinical features
Angiosarcoma, regardless of its genesis usually begins as a very poorly defined red plaque resembling a bruise (1046). Lesions can become quite large before metastasis occurs. When it does, the spread is usually haematogenous. Its borders may extend for several centimetres beyond what is visible (1969). Areas of nodularity arise after a time, but not in all patients. Unless a lesion is detected very early, multiple relapses and death are frequent occurrences.

Histopathology
Angiosarcoma begins as a plaque, with small, jagged thin walled vessels that insinuate themselves between collagen bundles of the reticular dermis. Unlike in Kaposi sarcoma, there is no tendency of spindled cells to first appear in increased number around pre-existent vessels and/or adnexa. The endothelial cells become progressively more protuberant, with enlarged, hyperchromatic nuclei. Lymphoid nodules are sometimes seen. The edges of plaques of angiosarcomas can be very poorly demarcated, making it practically impossible to provide accurate information about the resection margins. Plaques of spindled endothelial cells in the post-mastectomy setting are not necessarily those of angiosarcoma, as Kaposi sarcoma can also occur (59). The plaque stage of angiosarcoma can give rise to nodules, composed of compact masses of spindled or epithelioid cells, or both. Vascular lumina may be hard to detect in such nodules, and careful inspection may be needed to differentiate these from melanoma and spindle cell squamous carcinoma if only a partial biopsy is submitted. Cytoplasmic vacuoles may be a clue to endothelial differentiation in poorly differentiated cases.

Immunohistochemistry
The cells of angiosarcoma are usually positive for CD31, CD34 or VWF(VIIIrAg). Poorly differentiated tumours can lose one or more of these antigens, necessitating a panel in difficult cases (1755). Recently FLI-1 has been described as a useful marker with the additional advantage of nuclear staining (761). Angiosarcoma in the post-mastectomy setting may show blood vascular differentiation, despite a pathogenesis related to lymphoedema (1277). Angiosarcomas are consistently negative for HHV-8 (1371).

Differential diagnosis
It includes the atypical vascular proliferation after radiation therapy, Kaposi sarcoma and pseudovascular squamous cell carcinoma.

Genetics
Cytogenetic changes include gains of 5pter-p11, 8p12-qter, and 20pter-q12, losses of 7pter-p15 and 22q13-qter, and −Y (2101). Insufficient numbers of cases have been analyzed to determine if there are reproducible differences between different types of angiosarcoma.

Prognosis and predictive factors
Metastases to regional lymph nodes and to the lungs occur, often after repeated local recurrences and surgical excisions. The prognosis is poor, and in one series, only 15% of patients survived for 5 years or more after diagnosis (1046). This, in part, reflects the delayed diagnosis of these lesions. This limited survival is despite the use of various treatment modalities, sometimes involving surgery, radiotherapy, and chemotherapy.

Fig. 5.13 Angiosarcoma of the upper arm in a patient with a previous carcinoma of the breast (Stewart-Treves syndrome).

Fig. 5.14 Cutaneous angiosarcoma. The blood vessels have swollen endothelial cells with hyperchromatic nuclei.
**Lymphangioma circumscriptum**

**Definition**
Lymphangioma circumscriptum refers to a vascular malformation involving the lymphatic vessels of the superficial dermis. A denomination as superficial lymphatic malformation would be more appropriate to describe this lesion.

**ICD-O code** 9170/0

**Epidemiology**
Usually, lymphangioma circumscriptum is present at birth or appears early in life.

**Localisation**
Lymphangioma circumscriptum may be located in any anatomic site, but has predilection for the axillary folds, shoulders, neck, proximal parts of the extremities and tongue (750,1798,2502). Lesions involving eyelids and conjunctiva (841) and genital skin of males and females (149,419,2006,2436) have also been described.

**Clinical features**
Clinically, the lesion consists of numerous small vesicle-like lesions, often with a verrucous surface, grouped in a plaque. Sometimes purplish areas within the lesion are seen due to haemorrhage and thrombus formation within the blood vessel component. Probably, the superficial vesicles are the result of saccular dilations of superficial lymphatics secondary to raised pressure transmitted from the underlying pulsating cisterns (2502). Magnetic resonance imaging accurately demonstrates the true extent of involvement (1541). In rare instances, superficial lymphatic malformations are associated with visceral lymphatic malformations involving the mediastinum (1643) or the bladder wall (1107). Additional associations include Becker naevus (1762), and superficial lymphatic malformations have been described in patients with Maffucci syndrome (2292) and Cobb syndrome (2168).

**Macroscopy**
The excised specimens of lymphangioma circumscriptum show dilated vascular spaces involving both the superficial dermis and deeper subcutaneous tissue, which correspond to the malformed lymphatic vessels.

**Histopathology**
The stereotypical superficial lymphatic malformation is accompanied by deep lymphatic dilated cisterns with muscular walls situated in the subcutaneous fat, resulting in swelling of the tissue beneath the superficial vesicles (1768). The superficial component consists of dilated lymph vessels, lined by flat endothelial cells in a discontinuous layer, and situated in the papillary dermis, and the superficial reticular dermis (179,750).

Sometimes, the lymphatic vessels are arranged in clusters in the papillary dermis, resulting in a papillated or verrucous skin surface. The vessels may contain homogeneous eosinophilic proteinaceous lymph or blood, and occasionally foamy macrophages. Scattered lymphocytes may be seen in the connective tissue stroma between dilated lymphatic vessels. In extensive lesions, large irregular lymphatic channels are usually seen beneath the superficial vessels in deep reticular dermis and subcutaneous fat.

**Immunohistochemistry**
The usual immunohistochemical markers for endothelial cells, such as factor VIII-related antigen, Ulex europaeus, and CD31 do not differentiate between blood and lymphatic vessels (1799). In these cases, new endothelial cell markers such as vascular endothelial growth factor receptor-3 (VEGFR-3) (763,1463), D2-40

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**Fig. 5.15** Lymphangioma circumscriptum. **A** Close-up view of the lesions showed that it consisted of numerous vesicle-like lesions, some of them with a verrucous surface, grouped in a plaque. Purplish areas are seen due to haemorrhage and thrombus formation within a blood vessel component. **B** Histopathologically, the lesion consisted of dilated lymph vessels involving the superficial dermis and covered by hyperplastic epidermis with compact hyperkeratosis.
and Prox1 (2535) may be helpful, since these markers are expressed by lymphatic endothelium (763,1463).

**Histogenesis**
Lymphangioma circumscriptum results from abnormalities in the embryologic development of lymphatic vessels of the skin. Lymphangioma circumscriptum probably represents sequestered dermal lymphatic vessels that failed to link up with the rest of the lymphatic system (2502). However, an ultrastructural study suggested that lymphangioma circumscriptum was induced by long-standing lymphatic stasis (103). In some patients, lymphangioma circumscriptum has developed after surgery or radiotherapy on the involved area (1406,1859).

**Prognosis and predictive factors**
Usually, lymphangioma circumscriptum is a localized and superficial lymphatic malformation that only causes cosmetic problems and does not require treatment. The presence of a deep component may explain the tendency of the lesions to persist after superficial excision.

**Progressive lymphangioma**

**Definition**
Progressive lymphangioma is a benign, localized, slow-growing neoplasm composed of thin-walled, interconnecting vascular channels in the dermis and subcutis.

**ICD-O code**
9170/0

**Synonyms**
Acquired progressive lymphangioma, benign lymphangioendothelioma.

**Epidemiology**
Progressive lymphangioma is rare. It occurs chiefly in middle-aged or older adults and does not show a sex predilection (918).

**Etiology**
Progressive lymphangioma has been reported after trauma, such as surgical procedures and tick bites. Inflammation secondary to trauma has been claimed to play a role (2463,2532).

**Localization**
Lesions have been reported most commonly on the lower extremities, but any region of the skin may be affected (918).

**Clinical features**
Lesions usually present themselves as solitary, well-circumscribed, red or violaceous patches or plaques. Although usually asymptomatic, patients may complain of tenderness, pain, or itching. Because of slow growth over years, lesions may measure several centimetres in diameter (918,1157).

**Histopathology**
Progressive lymphangioma is characterized by delicate, often widely dilated vascular spaces lined by a monolayer of monomorphous endothelial cells. In some foci, endothelium-lined papillary stromal projections extend into those spaces. With progressive extension into the deep dermis, vascular spaces become narrower. They tend to dissect between collagen bundles and to surround pre-existing vessels and adnexal structures. Endothelial cells are more numerous than in normal lymphatic vessels and may be closely crowded together. Nuclei may be hyperchromatic, but there is no prominent nuclear atypia.

**Immunohistochemistry**
Endothelial cells are usually stained by antibodies against CD31 and CD34, whereas other endothelial markers give more inconsistent results. Actin-positive pericytes around vascular lumina are present focally (918,1157).

**Differential diagnosis**
Lymphangioma-like Kaposi sarcoma dif-
fers from progressive lymphangioma by the presence of plasma cells, the invariable presence of HHV-8 and more classical areas of Kaposi sarcoma elsewhere in the lesion. The so-called atypical vascular proliferation following radiotherapy (benign lymphangiomatous papules) differs from progressive lymphangioma clinically and histopathologically by presenting as tiny vesicles and histopathologically by being associated with much wider spaces in the upper dermis. Moreover, these lesions are thought to represent lymphangiectasias, rather than a neoplastic process (628,1921).

Histogenesis
Progressive lymphangioma is considered to be a neoplastic proliferation of lymphatic vessels. A neoplastic nature is suggested by its slowly progressive course. Derivation from lymphatic endothelia has been suggested on the basis of rare erythrocytes within and around vascular lumina and absence of a peripheral ring of actin-positive pericytes in most vessels.

Prognosis and predictive factors
Following surgical excision, local recurrences are exceptional. Metastases do not occur. Regression of lesions after systemic therapy with corticosteroids and in the absence of any treatment has been reported (918,1577,2463).

**Lymphangiomatosis**

Definition
Lymphangiomatosis is characterized by a diffuse proliferation of lymphatic vessels that may involve bones, parenchymal organs, soft tissue, and skin.

**Synonyms**
Generalized lymphangioma, systemic cystic angiomatosis, multiple lymphangiectasias.

**Epidemiology**
Lymphangiomatosis is a rare disease occurring mainly in the first two decades of life. There seems to be no sex predilection (862,1882).

**Localization**
Lesions occur in the skin and the superficial soft tissues of the neck, trunk, and extremities. Most cases of lymphangiomatosis affect bones and parenchymal organs, especially the lung, pleura, spleen, and liver. Soft tissue involvement occurs in the mediastinum and retroperitoneum.

**Clinical features**
Cutaneous and subcutaneous lesions present themselves as soft, fluctuant swellings that can be squeezed from one area to another and that may be associated with tiny vesicles. In patients with involvement of bones and visceral organs, the presenting signs range from pathologic fractures to chylothorax, chylous ascites, and other symptoms related to particular organs affected by the process. The interconnected lymphatic channels can be visualised by lymphangiography or direct injection of contrast media into cystic vascular spaces. Plain x-rays often reveal osteolytic areas as a consequence of involvement of bones (862,1882).

**Histopathology**
Cutaneous lesions of lymphangiomatosis are characterized by markedly dilated lymphatic channels throughout the skin and subcutis that are lined by a single attenuated layer of flattened endothelial cells and usually appear empty. Those channels tend to dissect between collagen bundles and to surround pre-existing structures in a manner reminiscent of well-differentiated angiosarcoma. Unlike angiosarcoma, cytologic atypia, endothelial multilayering, and mitotic figures are absent. The stroma often contains numerous siderophages and focal aggregates of lymphocytes. Exceptionally extramedullary haematopoiesis may be seen.

**Histogenesis**
Lymphangiomatosis probably represents a vascular malformation, rather than a neoplastic process.

**Prognosis and predictive factors**
When present on the neck and trunk, lymphangiomatosis of soft tissues is usually associated with extensive osseous or visceral involvement and carries a grave prognosis with a high rate of mortality (1882). In lymphangiomatosis of the limbs, involvement of bones and visceral organs is usually insignificant and prognosis, therefore, favourable (1021).
Smooth muscle is found in the skin in the arrector pili muscles, the walls of blood vessels and in ‘genital’ skin, which includes the scrotum (dartos muscle), vulva and nipple (areolar smooth muscle). Each of these sites of smooth muscle can give rise to a tumour. Tumours of striated muscle are exceedingly rare in the skin. Only the rhabdomyomatous mesenchymal hamartoma (striated muscle hamartoma) will be considered below.

**Smooth muscle hamartoma**

**Definition**
Smooth muscle hamartoma is a proliferation of dermal smooth muscle bundles that is usually congenital.

**Synonyms**
Arrector pili hamartoma, congenital pilar and smooth muscle naevus, congenital smooth muscle naevus

**Epidemiology**
Smooth muscle hamartoma is usually congenital with only occasional reports of lesions with onset in adolescence or adulthood (590,1069). There is a slight male predominance. The lesion is uncommon (1028).

**Localization**
The lesions are most often located on the trunk and extremities, particularly proximally (1145). Cases have been reported involving the head and neck region (1290), scrotum (1870) and conjunctiva (1966).

**Clinical features**
The typical presentation is as a solitary patch or plaque of varying size, usually between 1 and 10 cm, which may show hyperpigmentation and/or hypertrichosis (1145) and which may increase in size with the growth of the patient (2610). A positive pseudo-Darier sign is seen in most cases (2610). Occasional cases have an atrophic appearance (886). Less common presentations may include papular follicular lesions (659), multiple lesions (915,2200) and the so-called “Michelin tyre baby”, the latter typically in boys. Patients with Michelin tyre syndrome may have various other associated abnormalities (2093). A clinical classification has been proposed in which type 1 refers to the usual localized form, type 2 the follicular variant, type 3 to multiple lesions and type 4 to the diffuse variant (819).

**Histopathology**
There are increased numbers of variably orientated discrete smooth muscle bundles within the dermis and sometimes the subcutis and these may connect to hair follicles (1145,2093). The overlying epidermis may show acanthosis and basal hyperpigmentation and there may be prominent folliculosebaceous units present, although these do not appear to be increased in number (206,1145).

**Immunohistochemistry**
Lesions have been positive for smooth muscle actin and desmin as expected (886,1299,2093). CD34 positive dendrocytes have been reported to be an integral part of the proliferation (1299).

**Differential diagnosis**
Becker naevus may show dermal changes identical to smooth muscle hamartoma. It has been suggested that these lesions may form a spectrum (1145).
Pilar leiomyoma differs from smooth muscle hamartoma in being acquired, frequently multiple, often painful and comprising less discrete smooth muscle bundles with intervening collagen.

**Genetic susceptibility**
Rare cases of smooth muscle hamartoma have been described in siblings and in a mother and her children (915). Xp microdeletion syndrome is characterized by an unbalanced translocation between the X and Y chromosomes leading to deletion of the distal short arm of the X chromosome. Affected infants show microphthalmia, linear skin defects and sclerocornea. The linear skin defects have been reported to show histological features similar to smooth muscle hamartoma (1794) although this was not described in another case (686).

A child with a familial paracentric inversion of chromosome 7q and Michelin tyre syndrome with smooth muscle hamartoma...
toma has been described. The relevance, if any, of the genetic abnormality is unknown (2093).

Pilar leiomyoma

Definition
Pilar leiomyoma is a benign tumour derived from the arrector pili muscle (1054,1878).

ICD-O code 8890/0

Synonym
Piloleiomyoma

Epidemiology
Solitary lesions have a female preponderance. They usually develop in adult life. Rarely, they are present at birth. Multiple lesions usually have their onset in the late second or third decades of life.

Localization
Solitary lesions may develop anywhere on hair-bearing skin, particularly the trunk and limbs. Multiple lesions have a predilection for the face, back and extensor surfaces of the extremities.

Clinical features
Pilar leiomyomas may be solitary or multiple, with up to several hundred lesions. Multiple lesions may be grouped, linear, or zosteriform. Solitary lesions may measure up to 2 cm or more in diameter, but multiple lesions are much smaller. Leiomyomas are firm reddish-brown papulonodules. Multiple lesions are usually painful; solitary lesions are infrequently so.

Histopathology
Pilar leiomyomas are circumscribed (but not sharply so), non-encapsulated tumours of the dermis, composed of bundles of smooth muscle arranged in an interlacing or haphazard pattern. The cells have abundant cytoplasm and elongated nuclei with blunt ends. Mitoses are infrequent or absent (1878). Atypical cells, similar to those seen in the symplastic leiomyoma of the uterus, are uncommon (1486). Granular cell variants are extremely rare (1586).

Small amounts of fibrous stroma are present between the muscle bundles in older lesions, but there is usually less stromal collagen than in the smooth muscle hamartoma. Overlying epidermal hyperplasia is sometimes present (1878). The tumour cells stain for desmin and smooth muscle actin.

Genetics
Some of the multiple cases are familial, with an autosomal dominant inheritance (728). The syndrome of multiple cutaneous and uterine leiomyomas is also autosomal dominant with the locus on chromosome 1q42.3-q43 (51,1526).

Cutaneous leiomyosarcoma

Definition
Cutaneous (dermal) leiomyosarcoma is a malignant neoplasm of smooth muscle cells arising in the dermis. Subcutaneous and soft tissue leiomyosarcomas are discussed in the soft tissue monograph.

ICD-O code 8890/3

Epidemiology
Over 100 cases of dermal leiomyosarcoma have now been reported (1164). Most cases develop in adults, with a peak incidence in the sixth decade. Childhood cases are extremely rare (2563). There is a male predominance.

Localization
These tumours have a predilection for the extensor surfaces of the extremities and to a lesser extent the scalp and trunk (593).

Clinical features
Dermal leiomyosarcomas are solitary, firm nodules measuring 0.5-3 cm in diameter. They are usually asymptomatic, but pain and tenderness have been recorded.

Histopathology
By definition, the major portion of the tumour is in the dermis, although subcutaneous extension is present in some cases. They have an irregular outline with tumour cells infiltrating into, or blending with the collagen fibres at the periphery. The tumour is composed of interlacing bundles of elongated spindle-shaped cells with eosinophilic cytoplasm and blunt-ended nuclei. Sometimes there is a suggestion of nuclear palisading. There is at least one mitosis per 10 high-power fields in cellular areas. Pockets of greater mitotic activity (mitotic ‘hot spots’) are found, usually in areas showing nuclear pleomorphism. Granular cell, epithelioid, inflammatory and desmoplastic variants have all been described (2476).

Two different growth patterns have been described: A nodular pattern which is quite cellular with nuclear atypia and many mitoses; and a diffuse pattern which is less cellular with well-differentiated smooth muscle cells and inconspicuous mitoses (1164).

Fig. 5.21 Leiomyosarcoma, confined to the dermis. There are bundles of spindle shaped cells and scattered mitotic figures. Not the nuclear pleomorphism.
Immunohistochemistry
The cells express smooth muscle actin. Desmin is present in the majority of cases. Pan-muscle actin (HHF-35) is sometimes present focally.

Histogenesis
The majority of tumours are derived from the arrector pili muscles. Rare cases derived from areolar smooth muscle in the nipple (1452) and dartos muscle in the scrotum (758) have been reported.

Genetics
An unequivocal genetic fingerprint for these tumours is currently lacking (2175). Various genes have been identified that are expressed differentially in tumour and normal tissue. Soft tissue leiomyosarcomas most often show genomic alterations in the 13q4-q21 region (622).

Prognosis and predictive factors
Dermal leiomyosarcomas may recur locally, but the reported incidence (5-30%) varies widely (2476), but metastases of confirmed cases are unknown (1139).

Rhabdomyomatous mesenchymal hamartoma
Definition
Rhabdomyomatous mesenchymal hamartoma (RMH) refers to single or multiple, congenital, frequently polypoid lesions that typically arise near the midline of the head and neck. They contain skeletal muscle fibres within the dermis (1618).

Synonyms
Striated muscle hamartoma (1008), congenital midline hamartoma.

Epidemiology
About 25 examples of this lesion have been reported (1973,2320). Typically, the lesions have been present since birth or early childhood, and most patients are children. Rare cases have been reported in adults (2037). Thus far, the male: female ratio is 2:1.

Etiology
These lesions may be derived from striated muscle of the branchial arch (105, 899,1008,1973).

Localization
RMH typically arises in the midline of the head and neck, with a particular predilection for the nose and chin. There have also been cases involving the preauricular region (1902,2010,2122), lateral forehead (1973), and cheek (2320).

Clinical features
The majority of lesions are described as papules or polyps, but a few have presented as nodules (105,1973,2320) or “sessile masses” (1685). RMH lesions are generally asymptomatic, but they can demonstrate the interesting property of contractile motion, spontaneously or during crying or feeding (1973,2010). Most patients lack other congenital anomalies, but there have been associations with cleft lip and palate, ocular abnormalities (coloboma, microphthalmia, limbal dermoid), low-set ears, craniofacial clefts, thyroglossal duct sinus, lipoma of the brain, and upper extremity and syndactyly (1008,1902,1973,2010,2037). Histologic features of RMH have been found in the cutaneous polyps (2037) of a case of Delleman syndrome, which consists of orbital cysts, cerebral malformations, and focal dermal hypoplasia as well as cutaneous appendages (723). In addition, a patient (1902) with RMH in association with ipsilateral limbal dermoid and coloboma (Goldenhar syndrome), has been reported.

Initially, it was believed that RMH might be an X-linked disorder, as the first few cases were reported in males, but this...
was not substantiated when a number of examples were described in girls. Thus far, familial occurrence of this lesion has not been documented.

**Histopathology**
The most striking feature is the presence of intersecting bundles of mature skeletal muscle fibres, with demonstrable cross striations, and with a general orientation perpendicular to the surface epidermis. Varying amounts of collagen and mature fat surround these muscle fibres (2037). They extend through the reticular dermis and become attenuated in the papillary dermis (1618), where they appear to surround adnexal structures, particularly vellus follicles and sebaceous glands (678,713,1618). Sebaceous and eccrine sweat glands are usually observed, and in one case there were ectopic apocrine glands (2320). Nerve elements in these lesions vary considerably; in some cases they are not prominent (2010), but in others there may be numerous small nerve twigs (987) or a large nerve bundle in the central core of the lesion (2037). One example contained elastic cartilage (2037), and calcification or ossification have also been reported (2010). In some cases, elastic fibre distribution has been reported to be normal (1618), while in others these fibres are markedly decreased (2037).

**Immunoprofile**
Skeletal muscle fibres in RMH stain positively for actin, desmin and myoglobin (678,899).

**Differential diagnosis**
Although RMH bears a resemblance to fibroepithelial polyp, naevus lipomatosus, and accessory tragus, the combination of midline location and a microscopic skeletal muscle component should permit distinction from those lesions (though small amounts of skeletal muscle have been reported in accessory tragi) (324)). Deeper or more primitive tumours such as fetal rhabdomyoma, fibrous hamartoma of infancy, or neuromuscular hamartoma (benign Triton tumour) should not be difficult to distinguish from RMH (678,2010).

**Somatic genetics**
There has been speculation about a human homolog of the mouse disorganization gene (Ds), which is responsible, directly or indirectly, for the development of hamartomas and other defects (1973,2242).
Keloid scar

Definition
Keloid scars are raised scars that extend beyond the confines of the original wound.

Epidemiology
Keloid scars occur with equal frequency in men and women. They affect all races, but are more common in dark-skinned individuals. In Black, Hispanic, and Asian populations, the incidence ranges between 4.5 and 16%. Keloids occur chiefly in persons under 30 years of age (1711,2149).

Etiology
There is a genetic predisposition to the formation of keloid scars. Moreover, hormonal and immunological factors may play a role. Keloids often appear in puberty and tend to enlarge during pregnancy; they have been claimed to be more common in patients with signs of allergy and increased serum levels of IgE. Wounds subjected to great tension or become infected are more likely to heal with a keloid scar (1711,2149).

Localization
Keloids are most common on the earlobes, cheeks, upper arms, upper part of the back, and deltoid and presternal areas. They are seen only rarely on the genitalia, eyelids, and on palms and soles (1711,2149).

Clinical features
Keloids are well-circumscribed, firm, smooth-surfaced erythematous papules or plaques that occur at the site of an injury. The preceding injury may be only minor and, therefore, not always apparent (e.g., rupture of an inflamed hair follicle). Older lesions may be pale or hyperpigmented. Especially in early stages, keloids are often itchy, tender, or painful (1711,2149).

Histopathology
After a prolonged period of wound healing thick, homogeneous, strongly eosinophilic bundles of collagen, in haphazard array, develop (1498). Those “keloidal” collagen bundles are the histopathologic hallmark of keloid scars, but are not seen in many cases fulfilling the clinical definition of keloids. The border of keloids is often irregular, with tongue-like extensions of bands of thickened collagen underneath normal appearing epidermis and superficial dermis.

Histogenesis
Keloid scars are characterized by an enhanced proliferation and metabolic activity of fibrocytes that seems to result, in part, from the excess of various cytokines produced by inflammatory cells, including transforming growth factor-b1 and platelet-derived growth factor. Moreover, a deficiency of cytokines that down-regulate collagen synthesis and inhibit proliferation of fibrocytes, such as interferon-a, has been noted. There is also evidence of reduced degradation of collagen caused, in part, by inhibition of collagenase activity through acid mucopolysaccharides, proteoglycans, and specific protease inhibitors (1686,1711,2149,2551).

Genetic susceptibility
Keloidal scar formation may run in families. It is also more common in Black individuals. A relationship with various human leukocyte antigens has been reported (1711).

Prognosis and predictive factors
The clinical and histopathologic features of keloid scars indicate a high probability of recurrence following surgical excision alone. Recurrence rates of 45-100% have been described (1711).

Hypertrophic scar

Definition
Hypertrophic scars are raised scars that do not extend beyond the confines of the original wound. As such, they are closely related to keloids, both being examples of a disturbance of wound healing leading to the formation of exuberant fibrous tissue. Whether hypertrophic scars are simply a less severe variant of keloid scars or represent a different pathologic process is controversial.

Epidemiology
Hypertrophic scars are common. The incidence of hypertrophic scarring (including keloid scars) ranges between 39 and 68% after surgery and between 33 and 91% after burns, depending on the depth of the wound (1711).

Localization
Hypertrophic scars are most common above the flexor aspects of joints and on the abdomen (2149).

Clinical features
By definition, hypertrophic scars differ from keloid scars by remaining confined to the original wound. Other distinguishing features are earlier manifestation of
hypertrophic scars (usually within 4 weeks after injury, whereas keloids may manifest themselves several months later), a tendency to regression and to contractures not seen in keloid scars, a lower tendency to recur after surgery, and different sites of predilection. In other respects, the clinical features of hypertrophic and keloid scars are essentially the same (2149).

**Histopathology**

Hypertrophic scars differ from normal scars chiefly by presence of nodular aggregates of collagen with many fibrocytes. The main distinguishing feature from keloid scars is the absence of keloidal (i.e., thick, strongly eosinophilic) bundles of collagen. Moreover, unlike keloid scars, hypertrophic scars show prominent blood vessels arranged perpendicularly to the skin surface. Borders of hypertrophic scars tend to be more regular, and nodules of collagen tend to be distributed more evenly.

**Differential diagnosis**

Keloids show thick hyaline collagen bundles. Cases with overlap features between keloids and hypertrophic scars are seen.

**Histogenesis**

No principal differences have been noted in the histogenesis of hypertrophic scars and keloid scars (1711).

**Prognosis and predictive factors**

Although hypertrophic and keloid scars are closely related, the distinguishing features, clinically and histopathologically, allow a judgment to be made about the probability of recurrence following surgical excision. In one series, the recurrence rate of hypertrophic scars was 10%, as opposed to 63% in keloid scars (257).

**Dermatomyofibroma**

**Definition**

Dermatomyofibroma is a distinct biologically benign fibroblastic/myofibroblastic cutaneous proliferation occurring frequently, but not exclusively in young female patients.

**ICO-O code**

8824/0

**Synonym**

Plaque-like dermal fibromatosis

**Epidemiology**

Dermatomyofibroma represents a relatively rare cutaneous mesenchymal neoplasm and usually occurs in young women. Infrequently, dermatomyofibroma is seen in male patients (1073,1189, 1581) and children (1654,1970).

**Localization**

Most cases of dermatomyofibroma arise in the shoulder and axilla regions, fol-
**Infantile myofibromatosis**

**Definition**
Infantile myofibromatosis (IM) is a tumour of the skin and soft tissues of disputed histogenesis, which is solitary in two thirds of cases. Multicentric lesions (myofibromatosis) occur (634A).

**ICD-O code** 8824/1

**Synonyms**
Solitary cutaneous myofibroma.

**Historical annotation**
IM was described by Chung and Enzinger in 1981 as a proliferative disorder of myofibroblasts (486). Cases had been described earlier as congenital fibrosarcoma (2529), congenital generalized fibromatosis (1229) and congenital mesenchymal hamartoma (203).

**Epidemiology**
Most lesions are present at birth, or appear in the first 2 years of life; onset in adults also occurs (2541). There is a male predominance.

**Clinical features**
About a third of lesions are situated in the deep soft tissues and the remainder are located in the skin and/or the subcutaneous tissues (1778). The head, neck and trunk are the usual sites. They measure 0.5 to 7 cm or more in diameter; they are greyish-white in colour, and fibrous in consistency.

**Histopathology**
The nodules are reasonably well circumscribed, although there be an infiltrative border in the subcutis. There are plump to elongated spindle cells, grouped in short fascicles. Delicate bundles of collagen separate or enclose the cellular aggregates. Mitoses are variable in number, but not atypical (486,753).

**Immunoprofile**
Tumour cells stain variably for actin and alpha-smooth muscle actin (1189,1581). As in other myofibroblastic conditions, the expression of actin seems to be dependent on the age and activity of neoplastic cells, and only approximately 50% of cases are positive for this marker (1582). Lesional cells are negative for S-100 protein, CD34, desmin, and h-caldesmon (581,1074,1189,1581).

**Prognosis and predictive factors**
Complete excision is advised since these neoplasms may reach a considerable size.

**Sclerotic fibroma**

**Definition**
Sclerotic fibroma is a benign soft tissue tumour composed of eosinophilic collagen bundles arranged in a storiform pattern (1895).

**ICD-O code** 8823/0

**Synonym**
Storiform collagenoma

**Epidemiology**
Solitary sclerotic fibroma is rare and occurs in both sexes at any age, from infancy to adulthood. Multiple tumours are typical of Cowden disease, a rare genodermatosis.

**Localization**
Most frequent sites of involvement are the face, upper and lower extremities and trunk.

**Clinical features**
Sclerotic fibroma presents as a translucent, white, flesh-coloured or waxy nodule. It is usually unique and measures less than 1 cm. It has a slowly progressive growth, over months or years. The lesion is asymptomatic (1590,1895,2369).
**Histopathology**
The tumour is usually situated in the reticular dermis. It is sharply demarcated and it is composed of hyalinized bands of collagen with a decreased number of fibroblasts. The collagen fibres are thick, glassy and aligned in parallel bundles with a storiform pattern. Elastic fibres are absent. The proliferation tends to expand, pushing aside the normal dermal collagen without engulfing the adnexae (1590,1895,2369). Alcian Blue staining reveals an increased amount of mucopolysaccharide.

**Immunoprofile**
Staining for S100 protein, myelin basic protein and neuron specific enolase and desmin are negative (1590,1895).

**Prognosis and predictive factors**
Although the lesion is benign, it should be removed due to its tendency to expand.

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**Digital mucous cyst**

**Definition**
Two types of lesions both with a pseudocystic circumscribed dermal mucin deposition exist. In the more common type a connection with the underlying joint cavity can be demonstrated (ganglion type). The second type represents a focal mucinosis produced by fibroblasts (myxomatous type).

**Synonyms**
Myxoid pseudocysts of the digits, ganglion of the distal interphalangeal joint, digital focal mucinosis.

**Epidemiology**
Women are more often affected and patients are middle aged or elderly.

**Localization**
They typically occur on the dorsum of the fingers near the distal interphalangeal joint or near the proximal nail fold. The index fingers and thumbs are primarily affected. The toes are rarely involved (1148,2221).

**Clinical features**
The lesions are solitary, soft, smooth surfaced and usually not greater than 1.5 cm. A connection of the pseudocyst to the underlying joint can be demonstrated in the majority of cases by magnetic resonance imaging or injection studies with dye (599,1034). Osteoarthrosis is sometimes evident.

**Histopathology**
Myxomatous type: this variant has a large pseudocystic area with a myxomatous stroma with scattered spindle-shaped or stellate fibroblasts analogous to focal mucinosis in other areas of the body. The overlying epidermis is often attenuated. The mucin contains mucopolysaccharides which stain positively with alcian blue and colloidal iron.

Ganglion type: cystic spaces containing mucin with a collagenous fibrous wall characterize these lesions. Occasionally in some areas of the wall a synovial lining can be demonstrated.

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**Digital fibrokeratoma**

**Definition**
Digital fibrokeratoma is a benign fibrous tumour often accompanied by a hyperplastic epidermis that arises mostly in the periungual area.

**Synonyms**
Acquired ungual fibrokeratoma, periungual fibromas of tuberous sclerosis (Koenen tumours), subungual and periungual fibromas, acral fibrokeratoma.

**Epidemiology**
Most patients are adults. Males are affected more frequently than females (2429). More than half the patients with tuberous sclerosis develop about puberty multiple fibrokeratomas (2470).

**Localization**
The majority of lesions occur on a finger or a toe. Occasionally, lesions present on the palms or soles.

**Clinical features**
The patients usually present with a solitary lesion. Normally, tumours are small and measure 3-5 mm in diameter. A case of a huge lesion measuring up to 5 cm has been described (1181).

**Histopathology**
Digital fibrokeratoma is composed of dense collagen fibres, often with vertical orientation, with a variable number of mature fibroblasts and small blood vessels. A few inflammatory cells can be observed. There is often epidermal hyperplasia. In the stroma thin elastic fibres are present and hair follicles are absent. In a rare variant an oedematous and less dense stroma is found (1279,1280).

**Genetics**
In patients with tuberous sclerosis mutations in two different genes, TSC1 on
chromosome 9 and TSC2 on chromosome 16 have been identified (582).

**Pleomorphic fibroma**

**Definition**
Pleomorphic fibroma (PF) is a benign, polypoid or dome-shaped cutaneous neoplasm with cytologically atypical fibrohistiocytic cells (1188).

**ICD-O code** 8832/0

**Epidemiology**
PF occurs mostly in adults (39,1188).

**Localization**
They are located on the trunk, extremities, head (39,1188) and rarely the subungual region (983).

**Clinical features**
PF are asymptomatic, solitary, slowly growing, flesh coloured and non-ulcerated dome-shaped to polypoid papules from 4-16 mm. The clinical differential diagnosis includes acrochordon, neurofibroma, intradermal naevus and haemangioma. Although clinical behaviour is benign, lesions may locally recur when incompletely removed (1188).

**Etiology**
Degeneration, ischemia (808) or the paracrine influence of mast cells (1842) may create the cytologic atypia of PF (1188).

**Histopathology**
PF are circumscribed, dome-shaped to polypoid, hypocellular dermal proliferations of spindle and irregularly shaped stellate or multinucleate cells. Lesional cells have scant cytoplasm and large, pleomorphic, hyperchromatic nuclei with small nucleoli and rare mitotic figures. Foam cells are rarely present. Haphazardly arranged, hyalinized dermal collagen is admixed with moderate mucin. The collagenous bundles in pleomorphic sclerotic fibromas are more storiform and clefted (458,808,1523). Myxoid (1614) and sclerotic variants have been described (808,1523).

**Immunoprofile**
Lesional cells are positive for muscle specific actin, CD34 and rarely alpha-1 antichymotrypsin (1188,1988).

**Differential diagnosis**
The histologic differential diagnosis includes: atypical fibroxanthoma, variants of dermatofibroma, fibrosarcoma, fibrous papule of the face, angiofibroma, giant cell fibroblastoma, desmoplastic Spitz naevus and fibroepithelial polyp with monster cells (1188).

**Giant cell fibroblastoma**

**Definition**
Giant cell fibroblastoma (GCF) is a histologic variant of DFSP, which primarily affects children.

**ICD-O code** 8834/1

**Epidemiology**
GCF is a rare tumour that primarily affects children in the first decade of life, with a strong male predilection. Occasional cases have also been reported in adults (751).

**Localization**
GCF most commonly affects the trunk, shoulder region and groin (similar to DFSP), but other reported sites include the extremities and head and neck (971,2174,2338).

**Clinical features**
Giant cell fibroblastoma is described as a slow growing, firm, dermal or subcutaneous mass which is painless and asymptomatic.
Macroscopy
Grossly, GCF is a firm yellow or grey tumour with gelatinous or rubbery consistency and without haemorrhage or necrosis (751,2174).

Histopathology
GCF is usually a subcutaneous tumour, but it often extends into the overlying dermis. Cellularity is variable, but for the most part, GCF is a hypocellular neoplasm composed of wavy spindle shaped cells and scattered giant cells set within a stroma that varies from myxoid to collagenous to sclerotic and contains scattered mast cells. Scattered giant cells with hyperchromatic and angulated nuclei are characteristic. Most giant cells are multinucleated, but some are mononucleated. The nuclei of multinucleate cells are either conglomerated towards the centre of the cell or arranged peripherally, in a characteristic floret pattern. Irregularly branching “angiectoid” spaces which resemble the vascular spaces of lymphangioma are characteristic but are not seen in all cases. These are lined by spindle and multinucleate cells with morphology identical to those seen in the surrounding stroma. Cellular areas representing DFSP or less often pigmented DFSP (Bednar tumour) may be present. Recurrent lesions are uncommon, but when they occur, the lesions may show a pattern of DFSP. Fibrosarcomatous transformation of GCF has been reported in a recurrent lesion originally diagnosed as DFSP (1841).

Immunoprofile
The stromal and lining cells are CD34 positive, but negative for VWF (VIIIrAg), CD31, S100, actin, desmin, and EMA (971,2338).

Dermatofibrosarcoma protuberans
Definition
Dermatofibrosarcoma protuberans (DFSP) is a mesenchymal neoplasm of the dermis and subcutis, generally regarded as a superficial low-grade sarcoma (1605,2491).

ICD-O code 8832/3
Synonym
Progressive and recurring dermatofibroma.

Epidemiology
DFSP typically presents during early or middle adult life, with male predominance. However, there is evidence that many tumours may have begun during childhood and become apparent during young adulthood.

Localization
The tumour occurs most commonly on the trunk, including chest, back, and abdominal wall. Less commonly, the neoplasm is located on the proximal extremities; it rarely involves the distal extremities. The head and neck, especially the scalp, are also commonly involved. The vulva (1377) and parotid gland are unusual sites of involvement.

Prognosis and predictive factors
Like DFSP, GCF is a locally aggressive tumour of intermediate malignancy, with up to 50% local recurrence in the original series. Metastases from GCF have not been reported.

Fig. 5.31 Giant cell fibroblastoma. A Angiectoid space lined by hyperchromatic spindle and multinucleate giant cells. B CD34 highlights both the giant cells and the surrounding spindle cells.
Soft tissue tumours

Macroscopy
Most excised primary DFSPs are indurated plaques with one or more associated nodules. Multiple discrete, protuberant skin and subcutaneous tumours are more characteristic of recurrent neoplasms. Often, there is evidence of a surgical scar on the skin surface of the tumourous tissue. Ulceration may be present. The cut surface of the tumour is grey-white and firm, with occasional areas showing a gelatinous or translucent appearance, corresponding to microscopic areas of myxoid change. Haemorrhage and cystic change are sometimes seen. However, necrosis, a common feature of malignant fibrous histiocytoma, is rarely observed in DFSP. It is unusual to encounter DFSP confined solely to subcutaneous tissue without involvement of the dermis (629).

Histopathology
DFSP diffusely infiltrates the dermis, and invades into subcutaneous tissue, especially along the fibrous septa of fat. The epidermis is usually uninvolved. A grenz zone may be present. In a well-sampled specimen, the tumour shows some variation in histologic features. The centre of the tumour is typically composed of compact, uniform, slender, mildly atypical, spindle-shaped cells, arranged in a whorled, storiform, or cartwheel pattern. The tumour cells tightly encase skin appendages without destroying them. Nuclear pleomorphism is inconspicuous, and mitotic activity is low-to-moderate (<less than 5/10 HPF). Some tumours have a prominent myxoid matrix, and microscopic myxoid changes have been observed in both primary and recurrent tumours (368). Superficial areas of the neoplasm are less cellular, and spindle cells are separated by dermal collagen. The deep portion of the tumour shows a proliferation of spindle cells which expand fibrous septa and interdigitate with fat lobules, resulting in a honeycomb appearance. In some tumours, giant cells similar to those of giant cell fibroblastoma are seen. At times, peculiar myoid nodules may be present, which represent a nonneoplastic myointimal or myofibroblastic proliferation. Occasional foci may resemble a low-grade fibrosarcoma, with longitudinal fascicles of spindle cells demonstrating more prominent nuclear atypia and mitotic activity (but not greater than 5/10 HPF). Such areas have been seen in a minority of primary or recurrent lesions (853).

Immunoprofile
DFSP cells label diffusely and strongly with antibodies to CD34 and vimentin. CD34 positivity may be lost in nodular regions. P75 (low-affinity nerve growth factor receptor) has been reported positive in DFSP cells (853). Tumour cells are negative for S-100 protein, smooth muscle actin, desmin, keratins, and epithelial membrane antigen. Scattered Factor XIIIa positive cells may be present. Tenascin is negative at the dermoepidermal zone (DEZ) in DFSP (1180). Stromelysin 3 is not expressed in the cells of a DFSP in contrast to dermatofibroma in which it is invariably expressed (558).

Differential diagnosis
Benign and cellular fibrous histiocytoma or dermatofibroma (DF) can be differentiated from DFSP by the presence of epidermal (sometimes basal cell) hyperplasia, more prominent collagenous stroma, collagen trapping, and infiltration of the fibrous septa, but minimal extension into fat lobules. Immunostains are also helpful. DF contains a focally but not diffuse positive CD34 spindle cell component. P75 and stromelysin 3 are negative, and tenascin is positive at the DEZ in DF. Diffuse positivity for S-100 protein and the presence of Meissner-like corpuscles separate lesions of diffuse neurofibroma from DFSP. Malignant fibrous histiocytoma (MFH) exhibits a higher degree of cellular atypia, pleomorphism, and mitotic activity.

Fig. 5.32 Dermatofibrosarcoma protuberans. A DFSP presenting as two reddish nodules with focal ulceration. B Compact, uniform, spindle-shaped tumour cells arranged in a storiform pattern. C Tumour cells show a strong immunoreactivity for CD34.

Fig. 5.33 Dermatofibroma (fibrous histiocytoma) Cut surface with distinctive yellow colour.
than DFSP. Necrosis is usually not a feature of DFSP, but is generally seen in MFH. Myxoid liposarcoma is distinguished from myxoid forms of DFSP by the presence of lipoblasts, negative CD34 staining, and deep soft tissue involvement.

**Histogenesis**

DFSP and its variant, giant cell fibroblastoma (GCF) are currently classified as neoplasms derived from fibroblasts. CD34 labelling suggests a close linkage to dermal dendrocytes.

**Somatic genetics**

DFSP and GCF exhibit an identical chromosomal translocation. See page 259.

**Prognosis and predictive factors**

As with GCF, DFSP has a significant risk of local recurrence. The average recurrence rate in reported cases treated by wide local excision (2-3 cm.) is 18%. A much higher recurrence rate (43%) is reported in tumours treated by superficial or incomplete excisions only (853). Local recurrence usually develops within three years after initial surgery. Metastasis occurs rarely.

**Dermatofibroma (fibrous histiocytoma)**

**Definition**

Dermatofibroma (fibrous histiocytoma) (21) is an ill-defined, predominantly dermal lesion characterized by a variable number of spindle and/or rounded cells. A variable admixture of inflammatory cells, coarse collagen bundles in haphazard array, and variable epidermal, melanocytic and folliculosebaceous hyperplasia are present.

**ICD-O code**

8832/0

**Synonyms**

Histiocytoma (cutis) (2134), fibroma durum, subepidermal nodular fibrosis or sclerosis (1602), sclerotic or sclerosing fibroma (1895), sclerosing haemangioma (910).

**Epidemiology**

Dermatofibroma is a very common lesion and may develop at any age, but particularly during the third and fourth decades. The gender distribution varies among different populations.

**Etiology**

The etiology has not been established unequivocally. It is controversial whether it is an inflammatory (21,2590,2591) or neoplastic process (365,518,522,919). Dermatofibroma has been reported following local injuries such as trauma, insect bites or folliculitis, suggesting an inflammatory etiology. By contrast some examples have been reported to be clonal, supportive of a neoplastic etiology (457,1078,2422).

**Clinical features**

Most lesions are single, round, oval to targetoid papules. Early lesions are reddish, but older ones are brown to skin coloured, frequently with a brown rim at the periphery. They usually evolve rapidly. Dermatofibromas are moderately well circumscribed; the consistency usually is hard, but may be cystic, eroded or crust ed when secondary changes such as prominent haemorrhage, lipidization or trauma alter the lesions. Most lesions are flat, slightly elevated or show a shallow dell. The “dimpling” sign, when lesions are squeezed between the thumb and index finger, is characteristic. Occasionally, there may be a few, up to several dozen, sometimes grouped (“agminated”) papules. Multiple dermatofibromas are regarded as a marker of immune suppression; they have been observed in Black females with systemic lupus erythematosus; various other autoimmune disease such as Sjögren syndrome, pemphigus vulgaris, myasthenia gravis and ulcerative colitis treated with immunosuppressive drugs; occasionally in renal graft recipients or AIDS patients. Still other lesions form plaques or nodules to tumours. Dermatofibromas usually are long standing lesions which cause no symptoms.

**Macroscopy**

Gross examination reveals a moderately well-circumscribed, hard papule, nodule or tumour. The cut surface reveals a skin-coloured to distinctive yellow colour, which may show areas of haemorrhage and lipidization and then become cystic.

**Fig. 5.34** Dermatofibroma (fibrous histiocytoma). A Dermatofibroma with monster cells. B Clear cell dermatofibroma. Typical cytology with prominent collagen bundles.
Histopathology

Dermatofibromas show a dense infiltrate of spindle-shaped and/or round cells, some of which may be fibrocytes and/or macrophages, centred in the reticular dermis and sometimes, the upper part of the subcutis. Early lesions are rich in macrophages, some of which may be siderophages, and/or lipophages, others multinucleate, e.g. Touton or foreign body giant cells. Established lesions show prominent cellularity and coarse haphazardly arranged collagen bundles. They are frequently arranged in short fascicles that interweave (“storiform”), sometimes with a sclerotic centre.

Lesions are ill-defined and at the periphery there can be collagen trapping by lesional cells (“collagen ball formation”). Epidermal, melanocytic and folliculosebaceous hyperplasia is characteristically found above the lesions, and this can be so prominent that buds of hair follicles mimic superficial basal cell carcinoma. Rare cases show smooth muscle proliferation (1381). Lymphocytes are often spread throughout the lesion with frequent prominence at the periphery, but may be lacking in later stages. At times foam cells may be prominent in deeper areas adjacent to subcutaneous fat.

A wide number of variants of dermatofibromas have been proposed (369). Early lesions may show prominent proliferation of blood vessels, previously called sclerosing haemangioma (910), more recently haemangiopericytoma-like fibrous histiocytoma (2594). Prominent lipophages and siderophages are seen in the xanthomatous/histiocytic variant (1081,1114) and haemosiderorrheic variant (2036), respectively. Older lesions become progressively fibrotic, with shrinkage of the lesion, particularly seen in atrophic dermatofibromas particularly in the myofibroblastic variant (2593). Occasionally dermatofibromas are focally positive for CD34 (1840,2584). Recently, strongly 3 expression has been reported. It is not expressed in DFSP (558).

Immunoprofile

Dermatofibromas reveal a variable immunohistochemical profile: early lesions are rich in reactivity for macrophage markers such as PGM1 or KP1 (CD68), but also exhibit strong reactivity for factor XIIIa in both macrophages and fibroblasts (2590). This reactivity is mostly seen at the periphery and continuously diminishes with the ageing of the lesion to be completely absent in atrophic variants. Actin expression is variably seen in dermatofibromas in particular in the myofibroblastic variant (2593). Occasionally dermatofibromas are focally positive for CD34 (1840,2584). Recently, strongly 3 expression has been reported. It is not expressed in DFSP (558).

Differential diagnosis

The most important histologic differential diagnoses are dermatofibrosarcoma protuberans (particularly with the cellular variant of dermatofibroma) and Kaposi sarcoma. Dermatofibrosarcoma protuberans is poorly circumscribed, usually much broader and deeper with irregular dissection of subcutis, and shows cells with wavy nuclei in association with delicate fibillary bundles of collagen frequently arranged in a storiform pattern. In contrast to dermatofibroma it is regularly positive for CD34. Kaposi sarcoma in nodular and tumour stage is characterized by erythrocytes extravasated into slits between interweaving fascicles of spindle-shaped cells; often, tiny pink hyaline globules that represent degenerated erythrocytes are found in these spindle-shaped endothelial cells. Lesions are positive for CD34 and vascular markers such as CD31.

Variants

Aneurysmal fibrous histiocytoma

This is not uncommon (367,2054). It may rapidly enlarge because of spontaneous or traumatic haemorrhage into a previously unspectacular lesion or rarely de novo development, and frequently is painful. Clinically, it may mimic nodular melanoma or nodular Kaposi sarcoma. Histology reveals extravasation of erythrocytes, pseudovascular spaces and iron deposits. This histology may occasionally also be confused with melanoma or nodular Kaposi sarcoma, yet the absence of melanocytic as well as vascular markers in the spindle cells easily excludes these simulants.

Epithelioid cell histiocytoma

This lesion (840,1155), including a cellular variant (794) is rare. It occurs on the upper extremities and trunk as a skin-coloured to reddish-brown, hard, exophytic papule, frequently thought to be a Spitz naevus. Histology reveals a lesion mostly restricted to the papillary dermis, prominent epidermal hyperplasia (“colllarette”) and a sheet-like infiltrate of epithelioid to scolloped fibroblasts. These features may also closely simulate Spitz naevus, yet lesions are negative for melanocytic markers, but positive for factor XIIIa.

Cellular fibrous histiocytoma

This variant is rare (370). It occurs on the trunk or distal extremities and has a tendency to recur when incompletely excised. Histology reveals a dense, frequently deeply infiltrating lesion of spindle cells in an otherwise typical dermatofibroma. There may be moderate nuclear atypia, occasional mitoses and bizarre giant cells and these lesions have therefore also been called pseudosarcomatous or atypical fibrous histiocytomas (794). Exceptional cases of this variant have been reported to metastasize and, accordingly, they should always be completely excised.

Prognosis and predictive factors

The vast majority of lesions are benign. Occasionally incomplete excision may result in recurrence. The cellular and aneurysmal variants and lesions of the face may recur in a significant percent-age of cases (1583). Exceedingly rare cases of local aggressive growth or metastases to local or regional lymph nodes or even with wide spread metastases to lung have been recorded in the cellular variant.
Cutaneous neural tumours represent a small but important part of the cutaneous soft tissue neoplasms. Their histogenesis is conceptually analogous to their deep soft tissue or visceral counterpart, i.e., they recapitulate to variable extent the architectural and cytologic constituents of normal peripheral or autonomic nerves. Likewise, their classification is identical to their soft tissue counterparts. In this chapter, only those tumours are discussed which are particularly relevant for the dermatopathologist by their distinct morphology, predominant cutaneous manifestation, or their recent recognition and significance in the cutaneous pathology. These include the neuroendocrine carcinomas, rare but problematic peripheral variants of primitive neuroectodermal tumours, the non-neoplastic neuroma group with its spontaneous and reactive types and the recently defined, but still histogenetically controversial, nerve sheath myxoma-neurothekeoma spectrum.
WHO histological classification of neural tumours

|Primitive neuroectodermal tumour (PNET)| 9364/3 |
|Ewing sarcoma| 9260/3 |
|Nerve sheath myxoma| 9562/0 |
|Merkel cell carcinoma| 8247/3 |
|Granular cell tumour| 9580/0 |

1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) [786] and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of skin (Merkel cell) carcinomas

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>M - Distant metastasis</th>
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<tbody>
<tr>
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<tr>
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<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but no more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone</td>
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**Stage grouping**

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<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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</tbody>
</table>

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N - Regional lymph nodes

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</tr>
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<tbody>
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<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

1 For PNET and Ewing sarcoma see TNM table of soft tissue tumours
2 [784,2219].
3 A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.
Palisaded, encapsulated neuroma and traumatic neuroma

Palisaded, encapsulated neuroma

Definition
Palisaded, encapsulated neuroma (PEN) is considered a spontaneous proliferation of nerve fibres without evidence of previous trauma.

Synonyms
Solitary circumscribed neuroma, spontaneous neuroma, true neuroma

Historical annotation
The tumour was described by Reed et al. in 1972, who pointed out that despite the occasional nuclear palisading and encapsulation, the tumour is different from Schwannoma (1908).

Epidemiology
PEN is most common in the 5th and 7th decades and occurs in an approximately equal ratio in both genders. The majority of the lesions, about 90%, are located on the face, but they can occur anywhere on the body. Mucosal involvement has also been recorded (453,752,1908).

Clinical features
PEN usually manifests as a solitary, small (2-6 cm), skin-coloured or pink, firm or rubbery, dome-shaped, asymptomatic papule or nodule. There is no established association with neurofibromatosis (453,752,1908).

Macroscopy
On cut sections, the tumour is a yellow-pink, firm ovoid mass in the dermis.

Histopathology
On low magnification, PEN is a well-circumscribed, round or oblong nodule located in the dermis. It is surrounded by a thin fibrous capsule, which is poorly discernible or incomplete near to the epidermal aspect of the tumour. The tumour is composed of tightly woven fascicles which are separated by cleft-like spaces. The proliferating cells are slender spindle cells with ovoid, evenly chromatic nuclei and eosinophilic cytoplasm. A parallel arrangement of nuclei resembling a palisading pattern or rudimentary Verocay bodies is occasionally present. Mitotic figures are rare or absent. PEN lacks distinct fibrosis, inflammation or granulomatous reaction. A connection with the originating nerve usually requires serial sectioning of the tissue. Silver impregnation reveals numerous nerve fibres (axons), usually in parallel arrangement with the longitudinal axes of the fascicles (55,80,90,453,585,646,752,1314,1908).

Immunophenotype
The cells in the capsule stain for epithelial membrane antigen, whereas the spindle cells of the fascicles are positive for S-100 protein and collagen type IV. The axons are labeled with antibodies to neural filaments. Variable myelinization is detected by CD57 (Leu-7) and myelin basic protein (55,80,90).

Variants
Plexiform and multinodular types. These rare variants represent unusual growth pattern, but otherwise they retain the usual internal structures and composition of PEN (81,84).

Spontaneous, non-encapsulated neuromas
These tumours are part of the Multiple Mucosal Neuroma (MMN) syndrome, which is often part of the Multiple Endocrine Neoplasia syndrome (MEN2b), which is associated with pheochromocytoma and medullary carcinoma of the thyroid (815). The neuromas in MMN manifest as numerous, soft-rubbery, skin-coloured or pink papules and nodules around mucosal orifices, lip, eyelids, and tongue, but scattered cutaneous involvement can also occur (835,1658,1994). Musculoskeletal abnormalities and intestinal ganglieneuromato-

Fig. 6.1 Palisaded, encapsulated neuroma. A Multinodular variant of palisaded encapsulated neuroma. B The tumour is formed by compactly arranged fascicles separated by artificial clefts.
sis are also part of the syndrome (236,2504). Histologically, the tumour is composed of numerous tortuous or fascicular arrangements of hyperplastic nerve bundles infiltrating the submucosa or the dermis, hence the term “non-encapsulated neuroma” has also been applied. The individual fascicles have a linear, elongated appearance instead of the round or oblong structure of PEN; however, the constituent cells are identical to those seen in PEN. Occasionally perineurial and endoneurial increase of mucin can be noted. The immunohistochemical profile of this variant is similar to PEN (815, 835,1658,1994).

Genetics
Activated mutations of the RET proto-oncogene, involving the somatic or the germinal cell-lineage are found in both the inherited and acquired forms (466, 545,2310). However, MMN without genetic abnormalities have also been reported (1863,2379).

Prognostic factors
PEN and its variants are benign, and simple excision is a sufficient treatment. The mucosal neuromas of MEN2b often precede the manifestation of the other endocrine tumours. Therefore their correct recognition is important (1020).

**Traumatic neuroma**

Definition
Traumatic neuromas represent reactive or regenerative proliferation of the nerve sheath components as an attempt to reestablish lost nerve integrity after sharp or blunt physical trauma.

**Synonyms**
Amputation neuroma, supernumerary digit

**Epidemiology**
Traumatic neuromas can occur at any age or gender. The amputation type is more common on the extremities (1535). A special variant sometimes referred to incorrectly as “supernumerary digit” occurs on the lateral aspects of hands or feet of newborns. They represent amputation neuromas at the site of the in-utero separated extranumerary digit (487,2152).

**Clinical features**
Traumatic neuromas develop at the sites of previous trauma usually as solitary, skin-coloured, broad-based, firm papules and nodules. They are often sensitive or painful on pressure. Lancinating pain is characteristic of amputation neuromas (351,530,2342).

**Macroscopy**
Traumatic neuromas are firm, white-yellow, ill-defined dermal or subcutaneous masses often in a discernible association with the proximal nerve stump.

**Histopathology**
The tumour is composed of an irregular, haphazardly arranged proliferation of regenerating nerve fascicles of various sizes and shapes embedded in a fibrous stroma. Earlier lesions show acute and chronic inflammation, occasional granulomatous inflammation, whereas more established lesions are markedly fibrotic. Although the tumour is encased in the sclerotic stroma, there is no true encapsulation, and the distal end of the regenerating nerve fascicles often infiltrates the stroma (90,2084). The individual nerve fascicles appear to recapitulate the architecture of the normal nerve fascicles, but there is considerable variation in their diameter. The constituent cells
are slender spindle cells (Schwann cells, perineurial cells, and endoneurial fibroblasts). Silver impregnation reveals numerous nerve fibres (axons) in the tumour in a pattern approximating the normal 1:1 ratio of Schwann cells and axons. The “supernumerary digit” is a polypoid lesion covered by thick hyperorthokeratosis with a fibrous stalk containing regenerating nerve fascicles. The morphology of the regenerating nerve fibres is identical to the ones seen in other amputation neuromas.

Immunohistochemistry
The constituent spindle cells of the nerve fascicles are positive for S-100 protein, collagen type IV, whereas the surrounding perineurial cells, when present, stain for epithelial membrane antigen. Antibodies to neural filaments highlight the axons, and myelinization can be demonstrated by antibodies to myelin basic protein and CD57 (Leu-7).

Prognostic factors
Traumatic neuroma is a reactive lesion, however it can cause local interference with adjacent organs and is often symptomatic. The usual treatment is simple excision.

Fig. 6.4 Traumatic neuroma. A Supernumerary digit (amputation neuroma). Acral polypoid lesion with proliferation of nerve fascicles at the base of stalk. B Higher magnification of the regenerating nerve fascicles in the fibrous stroma. C The regenerating nerve fascicles show variation of diameter and orientation. The clear spaces correspond to increased perineurial mucin.
Primary malignant peripheral primitive neuroectodermal tumour (PNET) / Extraskeletal Ewing sarcoma (ES)

Definition
PNET/ES are malignant small blue round cell tumours, which exhibit varying degrees of neuroectodermal differentiation. In the past, they were regarded as separate entities, but recent cytogenetic and molecular genetic studies have proven that they represent two ends of a phenotypic spectrum of the same tumour type – Ewing sarcoma being relatively undifferentiated and PNET showing morphological (light microscopic/ultrastructural) and/or immunohistochemical features of neuroectodermal differentiation.

ICD-O codes
PNET 9364/3
Ewing sarcoma 9260/3

Synonyms
Peripheral neuroepithelioma, peripheral neuroblastoma

Epidemiology
Primary PNET/ES of skin and subcutaneous tissue are rare neoplasms. These tumours are mainly seen in children and young adults (median age 18 yrs), but they occasionally afflict elderly individuals. There is no significant sex predilection (72,82,138,449,978,1389,1791,1815,2050,2146,2210,2295,2328,2416).

Etiology
The etiology of this tumour is unknown.

Localization
These neoplasms have been described on the scalp, face, neck, shoulder, trunk and extremities.

Clinical features
The tumours usually present as ulcerated or non-ulcerated, often painless, but rarely tender, nodules. Occasionally, they appear polypoid (138,978). Not infrequently, they are clinically misdiagnosed as benign tumours or cysts. A case of cutaneous PNET with numerous tumour nodules that were present for several years has been documented (2050).

Macroscopic features
The tumours are greyish white and fleshy. Foci of haemorrhage are sometimes noted. Their sizes usually vary from 5 cm to 10 cm.

Histopathology
The tumours usually occupy the dermis with focal extension into subcutis. Some tumours are entirely subcutaneous in location. The overlying epidermis may become ulcerated. The margins may be pushing or infiltrative. The neoplastic cells are small, round to oval and contain hyperchromatic or vesicular nuclei and scanty pale eosinophilic or vacuolated cytoplasm with ill-defined borders. The nucleoli are indistinct or absent. The cells are arranged in sheets, lobules, nests and trabeculae. The mitotic activity and necrosis vary from case to case. Many dark apoptotic cells may be seen. Prominent fibrovascular septa are present in most lesions and some exhibit peritheliomatous or pseudopapillary arrangement of cells. Occasionally, the stromal blood vessels form glomeruloid tufts with prominent endothelial and myointimal cells. Microcystic, pseudoglandular and pseudovascular spaces are observed in many neoplasms. Homer Wright rosettes and neuropil are only rarely present. In atypical examples of this tumour, larger cells with prominent nucleoli, pleomorphic cells with irregular nuclei or groups of mononuclear or binucleate rhabdoid or plasmacytoid cells are seen. Prominent epidermal inclusion cysts within the tumour have been described in one case. Intracytoplasmic glycogen can be demonstrated in most cases. The reticulin stain reveals fibrils around groups of tumour cells. The differential diagnosis of this neoplasm includes deposits of lymphoma/leukaemia, Merkel cell carcinoma, metastatic small cell neuroendocrine carcinoma, metastatic neuroblastoma, primary or metastatic rhabdomyosarcoma, glomus tumour, small cell melanoma and rare types of sweat gland tumour such as eccrine spiradenoma and non-neuroendocrine small cell carcinoma. Attention to histological detail, immuno-histochemistry, EM studies and genetic analysis help to reach the right diagnosis.

Immunohistochemistry
Characteristically, the neoplastic cells exhibit positivity for CD99 (MIC2 gene product), β2 microglobulin, FLI-1 gene product, vimentin and one or more puta-
tive neural/neuroendocrine markers such as NSE, PGP 9.5, neurofilament proteins, synaptophysin and Leu-7. Usually the stain for chromogranin is negative. The CD99 positivity is usually strong, diffuse and membranous. The FLI-1 stains the nuclei of the neoplastic cells. Aberrant cytokeratin, desmin, GFAP, S100 protein and NKIC3 expression may be noted in scattered cells in some cases. The tumour cells are negative for LCA, B&T cell markers, myeloperoxidase, muscle specific actin, MYO-D1, myogenin, EMA and HMB 45 {138}.

**Electron microscopy**
At the Ewing end of the spectrum, the cells appear rather non-descript with round nuclei and scanty organelles. There is usually abundant glycogen. The PNETs show elongated interdigitating cytoplasmic processes with a few rudimentary junctions, intermediate filaments, microtubules and sparse membrane bound dense core neurosecretory granules (100-250 nm in diameter). No myofilaments, desmosomes or melanosomes are seen {138}.

**Genetics**
Around 90% of skeletal and extraskeletal PNET/ES exhibit a characteristic chromosomal translocation, t(11;22)(q24;q12). This results in the fusion of EWS gene on chromosome 22q12 with FLI-1 gene on chromosome 11q24. A small number of cutaneous cases have been subjected to cytogenetic/genetic studies and these have also demonstrated the typical genetic defects {978,1389}. An additional copy of chromosome 22 was detected in one case. Conventional cytogenetic study, FISH and RT-PCR techniques have been used to detect these abnormalities. Additional copy of chromosome 22 was detected in one case. Conventional cytogenetic study, FISH and RT-PCR techniques have been used to detect these abnormalities.

**Prognosis and predictive factors**
These neoplasms are aggressive with metastatic potential. The usual sites of metastasis are regional lymph nodes, lung, liver and bones. However, the cutaneous PNET/ES appear to have a better prognosis than their soft tissue counterparts, probably because they are detected early and can be resected adequately. Long term survival has been recorded in a few cases with or without radiotherapy and adjuvant combination chemotherapy {138,478,978,2328}. A prognostically relevant grading or staging system is not yet available for these neoplasms.

**Fig. 6.6** Primary PNET of skin. Electron microscopy of a cutaneous PNET: the cytoplasmic processes of the neoplastic cells contain intermediate filaments and microtubules (arrow). The inset shows a neurosecretory granule.
Neural tumours

Definition
These tumours encompass a spectrum of neuromesenchymal neoplasms characterized by proliferation of nerve sheath cells in a variable myxomatous stroma. They can be further classified into “classic” and “cellular” types.

ICD-O code 9562/0

Synonyms
Cellular neurothekeoma (used exclusively for the cellular variant), cutaneous lobular neuromyxoma, myxomatous perineuroma

Epidemiology
These tumours are rare. The "classic type" has been reported in middle-aged adults (mean 48.4), with predominance in females, of the head and neck areas and upper extremities (73,1865). The "cellular type" has been observed in younger adults (mean 24 yrs), more common in females, predominantly on the head and neck areas (88,99,161,371). However, both types can occur at any age and at any location (229,418,479, 1222,1674,1684,2355).

Clinical features
The "classic types" manifest as skin-coloured, pink, soft, rubbery papules and nodules, whereas the “cellular types” have a firmer, rather red-tan-brown appearance. Their size ranges between 0.5–2.0 cm. Both types are commonly asymptomatic, but may become sensitive or tender (73,88,99, 161,371,1865).

Histopathology
The “classic type” is usually a well-defined, multilobular or fascicular tumour located in the dermis with or without extension to the subcutis. The lobules contain abundant myxomatous stroma, which appear to be confined by a thin fibrous encapsulation. The mucin is connective tissue type acidic mucopolysaccharide and stains strongly with colloidal iron, which clears after hyaluronidase treatment. Within the mucinous stroma, there are sparsely distributed spindle, stellate, and polygonal cells without appreciable cytologic atypia. Mitotic figures are rare or absent (73,88,755,1865). The “cellular variant” shows an ill-defined, often infiltrative growth pattern involving the dermis and subcutis. The proliferating cells form fascicles and nests and are arranged in a plexiform or multilobular pattern. The constituent cells are mainly epithelioid type with ample eosinophilic cytoplasm and indistinct cytoplasmic membranes. The cells have large “bubbly nuclei” with prominent nucleoli. In a smaller percentage of the cases, the tumour is composed of spindle cells with plump or ovoid nuclei forming nests and whorls. In the “cellular type”, cytologic and nuclear atypia are more common and mitotic figures can be conspicuous. Myxoid material is usually scant or present only around the individual nests (88,99,161,371). In both the “classic” and “cellular types”, associated stromal changes, such as fibrosis, hyalinization of the collagen, patchy chronic inflammation, and angioplasia can occur. Changes showing transition between the “classic” and “cellular types” within the same lesion have been documented. A direct connection with nerve twigs can be demonstrated only rarely.

Immunohistochemistry
The stromal cells in the “classic” type stain strongly for S-100 protein, collagen type IV and weakly for neuron-specific enolase and CD57 (Leu-7). The capsule, when present, may label for epithelial membrane antigen. The “cellular” type does not have a specific or consistent phenotype. The cells show variable expression of PGP9.5, collagen type IV, NK1/C3, CD34, and occasionally smooth muscle specific actin and CD57 (Leu-7). Staining for S-100 protein is rare, and

Fig. 6.7 Nerve sheath myxoma (neurothekeoma). A Cellular neurothekeoma (cellular variant of nerve sheath myxoma). The tumour cells form nests and strands infiltrating the dermis. B Nerve sheath myxoma "classical type". Lobular and fascicular dermal proliferation with myxomatous stroma.
when present it is usually in lesions where there are elements of the “classical” type (87,88,99,161,371,798,1370, 2281,2454)

**Prognosis**
Both variants are considered benign tumours, although rare cases of the “cellular” type with concerning cytologic atypia and mitotic activity have been reported (231,357). Both tumours can recur after incomplete removal; therefore, a complete excision is recommended for treatment.

**Fig. 6.8** Nerve sheath myxoma (neurothekeoma). A Higher magnification of the lobules shows the mixture of variable cellularity and myxomatous changes. B The tumour nests are well defined, but not encapsulated and contain minimal or no mucin. The adjacent stroma is hyalinized. C Stellate, polygonal, and spindled cells are embedded in a markedly mucinous matrix.
Definition
Merkel cell carcinoma is a rare malignant primary cutaneous neoplasm with epithelial and neuroendocrine differentiation. Tumour cells share morphologic, immunohistochemical and ultrastructural features with Merkel cells, but a direct histogenetic link is unproven.

ICD-O code 8247/3

Synonyms
First described in 1972 by Cyril Toker as trabecular carcinoma (2357). Other synonyms include neuroendocrine carcinoma of the skin, primary small-cell carcinoma of the skin, and cutaneous APUDoma.

Epidemiology
The estimated incidence of Merkel cell carcinoma is about 470 new cases per year in the United States. The tumour most commonly affects Caucasians (0.23 annual age adjusted incidence per 100,000) and is exceptionally rare in black individuals (0.01 annual age adjusted incidence per 100,000) (1616). Merkel cell carcinoma is more common in men than in women with a ratio of 2.3:1. This tumour typically occurs on the sun-exposed skin of older adults with a median age at presentation of 69 years.

Etiology
Anatomic and geographic distribution of Merkel cell carcinoma imply sun exposure as a major risk factor. A relatively high incidence of this neoplasm in solid organ transplant recipients and in patients with human immunodeficiency virus infection point towards an etiologic role of chronic immunosuppression.

Localization
The majority of Merkel cell carcinomas arise on sun-exposed skin. The most frequently affected sites are the head and neck (50%) and extremities (40%) (843). The trunk and genitalia are involved in less than 10% of cases. Exceptional cases on mucosal surfaces have been recorded.

Clinical features
Most tumours are solitary and present as a painless dome shaped nodule or indurated plaque that is red, violaceous or skin-coloured and, at times, ulcerated. Growth is typically rapid over a period of weeks to months. Most lesions measure less than 2 cm in diameter.

Tumour spread and staging
Merkel cell carcinoma has a high incidence of local recurrence, regional lymph node metastasis and, ultimately, haematogenous and/or distant lymphatic spread (517). Clinical staging after histopathologic diagnosis should include at the minimum a chest x-ray and CT of the chest and abdomen to exclude other possible primary sites and to evaluate for the presence of metastatic disease. Merkel cell carcinoma in locations other
than the eyelid, vulva and penis is staged according to the TNM system for non-melanoma skin cancers.

**Histopathology**

Merkel cell carcinoma is a small blue cell neoplasm, composed of cells of uniform size with a round to oval nucleus and scant cytoplasm. Nuclear membranes are distinct, the chromatin is finely dispersed and nucleoli are usually inconspicuous. Mitotic figures and nuclear fragments are numerous. Focal spindle cell differentiation may be present. The tumour is centred on the dermis and frequently extends into the subcutaneous fat. The epidermis may be involved in a pagetoid fashion (1384) and in exceptional cases the tumour cells are entirely limited to the epidermis. Ulceration of the epidermis occurs in a subset of cases. This neoplasm forms diffuse sheets and solid nests in the dermis. A trabecular growth pattern, ribbons or festoons can be seen mainly in the periphery. Pseudorosette formation is rare. The dermis occasionally shows a desmoplastic response. Larger lesions may show zonal tumour necrosis and angiolymphatic involvement is commonly present around the primary neoplasm. Not infrequently, Merkel cell carcinoma occurs in intimate association with an in situ or invasive squamous cell carcinoma (2450). Biphenotypic differentiation with squamoid or eccrine foci or even tripartite differentiation with squamoid, glandular and melanocytic foci are described. Areas of partial or complete regression can be found (529).

The histopathologic differential diagnosis includes basal cell carcinoma, melanoma, lymphoma, eccrine carcinoma, poorly differentiated squamous cell carcinoma, metastatic neuroblastoma, primary peripheral primitive neuroectodermal tumour and metastatic neuroendocrine carcinoma.

**Immunohistochemistry**

Merkel cell carcinoma shows epithelial and neuroendocrine differentiation. Tumour cells express low molecular weight cytokeratins (detectable by specific or broad spectrum cytokeratins such as AE1/AE3, CAM5.2, pan-cytokeratin), epithelial membrane antigen and the epithelial marker BER-EP4. Cytokeratin 20 is a sensitive and quite specific marker for Merkel cell carcinoma (1604). The staining pattern for low molecular weight cytokeratins and CK20 typically is as paranuclear dots, but may also show cap-like paranuclear or diffuse cytoplasmic staining (1138). CK20 is useful in combination with thyroid-transcription factor-1 to differentiate between Merkel cell carcinoma (CK20 positive, TTF-1 negative) and small cell carcinoma of the lung (<10% CK20 positive, TTF-1 positive) (463). CK20 and broad spectrum cytokeratin are also useful for the detection of occult micrometastases in sentinel lymph nodes (2287). Markers of neuroendocrine differentiation include chromogranin, synaptophysin, neuron-specific enolase, bombesin, somatostatin, calcitonin, gastrin and others. Merkel cell carcinoma also expresses CD117, the KIT receptor tyrosine kinase (2284), and in approximately a third of cases CD99 (1707). The tumour cells are negative for leukocyte common antigen and S-100.

**Histogenesis**

The histogenesis of Merkel cell carcinoma is controversial. A direct histogenetic link between tumour cells and Merkel cells is unproven despite overlap in the morphologic, immunologic and ultrastructural features. Another theory postulates that Merkel cell carcinoma arises from a primitive epidermal stem cell with a capacity to differentiate towards neuroendocrine cells and keratinocytes.

**Somatic genetics**

A deletion on the short arm of chromosome 1 (1p36) is commonly observed and is shared with other neoplasms of neural crest derivation including neuroblastoma and melanoma (2208). Numerous other chromosomal abnormalities are described in Merkel cell carcinoma, the most common being trisomy 6, affecting nearly 50% of tumours. As of yet, no candidate oncogenes or tumour suppressor genes have been identified.

**Prognostic factors**

Diverse clinical prognostic factors include older age, location on head and neck, size greater than 2 cm, immunosuppression and advanced disease stage (517,843,2208). Adverse histopathologic and immunologic features include more than 10 mitotic figures per single high power field, small cell size, angiolymphatic invasion, and immunoreactivity for CD44 (1803).
Granular cell tumour

Definition
Granular cell tumours (GCT) encompass a cytologically similar, but etiologically and clinically diverse group of entities that are characterized by proliferation of large cells with granular-appearing eosinophilic cytoplasm. Herein, only the variant with direct or indirect evidence of peripheral nerve sheath association and common cutaneous manifestation is considered.

ICD-O code 9580/0

Synonyms
Granular cell Schwannoma, granular cell nerve sheath tumour, granular cell myoblastoma, Abrikossoff tumour

Historical annotation
The tumour was thought to be derived from skeletal muscle cells by Abrikossoff (1927). The association with nerve sheath differentiation was proposed by Feyrter (1935).

Epidemiology
GCT affects mainly adults (age 30-50), but can occur at any age. The male to female ratio is about 1:3; it is more common in African Americans than in Whites (78,245,1354). The tumour is characteristically solitary, and about 70% are located in the head and neck area, including 30% of these in the tongue. Other common locations are the breast and the proximal extremities. GCT usually involves the skin and subcutis; however, visceral involvement can also occur, primarily in the respiratory tract (larynx and trachea) and the gastrointestinal tract (oesophagus, large bowel, and anal area) (245). In about 10% of the cases GCT is multifocal, simultaneously involv-

Fig. 6.11 Granular cell tumour. A Reactive squamous pseudoepitheliomatous hyperplasia with prominent cytologic atypia mimicking squamous cell carcinoma. The granular cells are intermingled with squamous epithelial cells. B Granular cell tumour. The brightly eosinophilic granular cells form solid nests and strands infiltrating the dermis. C Granular cell tumour associated with a peripheral nerve. The granular cells have polygonal shape, distinct cytoplasm and eosinophilic granular cytoplasm with round, fairly uniform nuclei. D The large, ovoid, brightly eosinophilic globules surrounded by clear halo represent giant lysosomes.
ing the skin, submucosa, and viscera (577). Congenital presentation has also been reported. No definite association with neurofibromatosis type 1 has been established (1642,2577).

Clinical features
GCT usually presents as an asymptomatic or occasionally tender or pruritic, skin-coloured or brown-red, firm dermal or subcutaneous papulo-nodule, ranging in size from 0.5-3.0 cm in diameter. Verrucous changes of the surface epithelium are common, whereas ulceration is uncommon. The cutaneous tumours grow slowly; most symptoms are related to visceral locations.

Macroscopy
GCTs are nodular, but not encapsulated, and present as firm dermal or subcutaneous masses with a thickened or verrucous epidermal surface. On cut-surface the tumour has a pink-yellow, finely granular appearance (2084,2490).

Histopathology
The tumour forms poorly cohesive nests, strands, fascicles, and sheets of polygonal, pale eosinophilic cells in the dermis and subcutis. Commonly, the cells form indistinct delicate fascicles that infiltrate the dermal collagen and extend to the subcutaneous septa. A variant of GCT with a distinctly plexiform growth pattern has been documented (1392). Perineural spread is a common feature. The cells have an abundant granular, faintly eosinophilic cytoplasm with round, small, hyperchromatic nuclei. The fine, eosinophilic, intracytoplasmic granules correspond to lysosomes, which are PAS positive and diastase resistant. Occasional larger, brightly eosinophilic ovoid bodies surrounded by a clear halo can be identified within the granules representing residual “giant” lysosomes. Interspersed between the granular cells, there are spindle cells with fibroblast-like features and histiocyte-like cells often with triangular, coarsely granular eosinophilic lysosomes designated as “angulated bodies”. Nuclear pleomorphism, prominent nucleoli, and mitotic figures are uncommon. A characteristic feature of most cutaneous GCTs is the overlying pseudoepitheliomatous hyperplasia, which can be so extensive that it can mimic a verruca or a well-differentiated squamous cell carcinoma.

Immunohistochemistry
GCT expresses markers associated with both neural (S-100 protein, PGP 9.5, neuron specific enolase, laminin, NGFR, calretinin, peripheral myelin proteins, P2-P0, myelin basic protein, CD57) and histiocytic (CD68, α-1-antitrypsin) differentiation. The tumour cells are positive for vimentin. Most studies report a negative reaction for neural filaments and GFAP (246,743,1063,1487,1540,1714).

Variants
Granular cell epulis of infancy
This is a rare, polyloid tumour of the alveolar ridge of the gingiva of the new-born with a predilection for girls. The tumour has cytologic features similar to GCT, but lacks globular cytoplasmic inclusions, angulate body histiocytes, and contains a distinct plexiform capillary pattern. The immunohistochemical profile is also different; the lesions are negative for S-100 protein,NSE, laminin, MBP, CD57, and α-1-ACT (740,1367,1764,2528).

Malignant granular cell tumour
These are extremely rare and comprise less than 2% of all granular cell tumours. The age and sex distribution is similar to that of their benign counterparts, but they are more common on the extremities (particularly on the thighs) rather than the head and neck areas, or the oral mucosa. Malignant GCTs grow rapidly, often ulcerate, invade locally and tend to spread via extensive metastases. Histologically and cytologically two forms can be distinguished: the more common type of malignant GCT is essentially identical to the benign tumour. Since cytologic atypia or mitotic activity are not reliable biologic indicators, correlation of clinical data (large size, rapid growth, ulceration) with the histologic features (necrosis, spindling, and lymphocapillary invasion) should guide in the diagnosis of malignancy. Additional features cited as useful for predicting malignancy are vesicular nuclei with large nucleoli and a mitotic rate greater than 2 mitoses/10 HPF.

The second type of malignant GCT is quite rare; both the primary tumour and its metastases display histologic and cytologic characteristics of malignancy. The immunophenotype of malignant GCT is also similar to that of the benign tumour, however the proliferation markers (Ki-67) show increased labelling indices, and p53 expression is prominent (2084).

Genetics
Only limited genetic studies have been performed on malignant GCT of the soft tissue. This showed two clonal karyotypes. One atypical tumour was aneuploid and all 11 benign tumours were either diploid (9 cases) or hyperdiploid (2 cases) (627).

Prognosis and predictive factors
GCT is benign, however local recurrence is common due to incomplete removal complicated by the typical perineural spread. The malignant variants are aggressive tumours and usually have numerous local recurrences before distant spread. Their overall prognosis is poor, with metastases developing within two years in the majority of cases and there is close to 60% mortality within three years (2084,2490). Because of the potential for recurrence and the morphologic overlap between benign and malignant GCT, complete excision is recommended.
The study of familial cancer syndromes has led to the discovery of key genes that are important not only for the understanding of the mechanisms of genetic susceptibility but also for giving new insights into genetic and signaling pathways involved in sporadic cancers. Investigations into the rare skin disease xeroderma pigmentosum has led to the discovery of 7 DNA repair genes involved in the nucleotide excision repair pathway. Studies of these patients allowed us to understand the mechanism of DNA repair in the general population. Eventually, the in-depth analysis of the activity of these repair genes may allow us to define a subpopulation of individuals at higher risk of developing cancers in different organ sites.

This chapter contains a detailed description of clinical, pathological and genetic data of some major, well characterized inherited syndromes associated with skin cancer or other skin disorders.
## Table 7.1
Inherited disorders associated with skin abnormalities

<table>
<thead>
<tr>
<th>OMIM</th>
<th>Disease</th>
<th>Inheritance</th>
<th>Tumour types</th>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>278700</td>
<td>Complementation group A</td>
<td>AR</td>
<td>BCC SCC MM</td>
<td>9q22.3</td>
<td>XPA</td>
<td>XPA</td>
<td>Damaged DNA-binding interaction with TFIIH and XPF/XPG endonucleases</td>
</tr>
<tr>
<td>133510</td>
<td>Complementation group B</td>
<td>AR</td>
<td></td>
<td>2q21</td>
<td>XPB/ERCC3</td>
<td>XPB</td>
<td>3' A5 helicase in TFHII</td>
</tr>
<tr>
<td>278720</td>
<td>Complementation group C</td>
<td>AR</td>
<td></td>
<td>3p25.1</td>
<td>XPC</td>
<td>XPC</td>
<td>Damaged DNA-binding only involved in global genomic repair. Heterodimer</td>
</tr>
<tr>
<td>126340</td>
<td>Complementation group D</td>
<td>AR</td>
<td></td>
<td>19q13.2-3</td>
<td>XPD/ERCC2</td>
<td>XPD</td>
<td>Damaged DNA-binding only involved in global genomic repair. Heterodimer</td>
</tr>
<tr>
<td>60045</td>
<td>Complementation group E</td>
<td>AR</td>
<td></td>
<td>11q12-13</td>
<td>DDB1</td>
<td>XPE P127</td>
<td>5' A3 helicase in TFHII</td>
</tr>
<tr>
<td>600811</td>
<td>Complementation group E</td>
<td>AR</td>
<td></td>
<td>11p11-12</td>
<td>DDB2</td>
<td>XPE P48</td>
<td>Damaged DNA-binding only involved in global genomic repair. Heterodimer</td>
</tr>
<tr>
<td>278760</td>
<td>Complementation group F</td>
<td>AR</td>
<td></td>
<td>16p13-13-13</td>
<td>XPF/ERCC4</td>
<td>XPF</td>
<td>5' structure-specific endonuclease heterodimer with ERCC1</td>
</tr>
<tr>
<td>133530</td>
<td>Complementation group G</td>
<td>AR</td>
<td></td>
<td>13q32-33</td>
<td>XPG/ERCC5</td>
<td>XPG</td>
<td>3' structure-specific endonuclease. Stabilization of the open complex</td>
</tr>
<tr>
<td>603968</td>
<td>Xeroderma pigmentosum variant</td>
<td>AR</td>
<td></td>
<td>6p21.1</td>
<td>POLh</td>
<td>POL h</td>
<td>Translesion DNA polymerase</td>
</tr>
<tr>
<td>600160</td>
<td>Familial melanoma</td>
<td>AR</td>
<td>M M</td>
<td>9p21</td>
<td>CDKN2A</td>
<td>P16/INK4</td>
<td>Inhibits CDKs from phosphorylating Rb, thereby freezing cell cycle</td>
</tr>
<tr>
<td>123829</td>
<td>Familial melanoma</td>
<td>AR</td>
<td>M M</td>
<td>12q14</td>
<td>CDK4</td>
<td>CDK4</td>
<td>Activated protein kinase resistant to p16 inhibition; overphosphorylates</td>
</tr>
<tr>
<td>155600</td>
<td>Familial atypical mole-malignant melanoma syndrome (FAMM) / Dysplastic naevus syndrome (DNS)</td>
<td>AR</td>
<td>M M</td>
<td>1p36(?)</td>
<td>unknown</td>
<td>unknown</td>
<td>CDKN2A and CDK4 genes have been excluded</td>
</tr>
<tr>
<td>109400</td>
<td>Naevoid basal cell carcinoma syndrome</td>
<td>AD</td>
<td>BCC</td>
<td>9q22.3</td>
<td>PTCH1</td>
<td>PTCH1</td>
<td>Development gene ; regulates the Sonic Hedgehog signaling pathway</td>
</tr>
<tr>
<td>158350</td>
<td>Cowden disease b</td>
<td>AD</td>
<td>M H</td>
<td>10q23</td>
<td>PTEN/MAC1</td>
<td>MAMC1</td>
<td>Lipid/protein phosphatase</td>
</tr>
<tr>
<td>158320</td>
<td>Muir-Torre syndrome</td>
<td>AD</td>
<td>CSN</td>
<td>2p22</td>
<td>hMSH2</td>
<td>hMSH2</td>
<td>Involved in DNA mismatch repair</td>
</tr>
<tr>
<td>175100</td>
<td>Gardner syndrome a</td>
<td>AD</td>
<td>EC</td>
<td>5q21</td>
<td>APC</td>
<td>APC</td>
<td>Negatively regulates ß-catenin, a cytoskeletal and growth-promoting protein, and the WNT signaling pathway</td>
</tr>
<tr>
<td>131100</td>
<td>Multiple endocrine neoplasia 1</td>
<td>AD</td>
<td>M FA</td>
<td>11q13</td>
<td>M EN1</td>
<td>menin</td>
<td>Inhibitor of J un D-activated transcription</td>
</tr>
<tr>
<td>171400</td>
<td>Multiple endocrine neoplasia 2</td>
<td>AD</td>
<td>CLA</td>
<td>10q11.2</td>
<td>RET</td>
<td>RET</td>
<td>Tyrosine kinase receptor involved in signal transduction</td>
</tr>
<tr>
<td>605284</td>
<td>Tuberous sclerosis 1</td>
<td>AD</td>
<td>M SL</td>
<td>9q34</td>
<td>TSC1</td>
<td>hamartin</td>
<td>Interacts with tuberin and exhibits growth-inhibitory activity</td>
</tr>
<tr>
<td>191092</td>
<td>Tuberous sclerosis 2</td>
<td>AD</td>
<td>M SL</td>
<td>16p13.3</td>
<td>TSC2</td>
<td>tuberin</td>
<td>GTPase-activating protein for RAP1 and RAB5; interacts with hamartin</td>
</tr>
<tr>
<td>162200</td>
<td>Neurofibromatosis 1 b (von Recklinghansen disease)</td>
<td>AD</td>
<td>FTK</td>
<td>17q11.2</td>
<td>NF1</td>
<td>neurofibromin</td>
<td>Negatively regulates ras-family of signal molecules through GAP function : Tumour suppressor activity</td>
</tr>
<tr>
<td>101000</td>
<td>Neurofibromatosis 2 b</td>
<td>AD</td>
<td>ST</td>
<td>22q12.2</td>
<td>NF2</td>
<td>merlin</td>
<td>Integrates cytoskeletal signaling</td>
</tr>
<tr>
<td>210900</td>
<td>Bloom syndrome b</td>
<td>AR</td>
<td>ST</td>
<td>15q26.1</td>
<td>BLM/RECL3</td>
<td>BLM</td>
<td>DNA helicase ; unwinds DNA at blocked replication forks</td>
</tr>
<tr>
<td>175200</td>
<td>Peutz-Jeghers syndrome</td>
<td>AD</td>
<td>M ML</td>
<td>19p13.3</td>
<td>STK11</td>
<td>STK11</td>
<td>Serine/threonine protein kinase : Tumour suppressor activity</td>
</tr>
<tr>
<td>268400</td>
<td>Rothmund-Thomson syndrome b</td>
<td>AR</td>
<td>D</td>
<td>8q24.3</td>
<td>RECL4</td>
<td>RECL4</td>
<td>DNA helicase ; unwinds DNA at blocked replication forks/recombination sites</td>
</tr>
<tr>
<td>277700</td>
<td>Werner syndrome b</td>
<td>AR</td>
<td>SSC</td>
<td>8p12</td>
<td>WRN/RECL2</td>
<td>WRN</td>
<td>DNA helicase ; unwinds DNA at blocked replication forks/recombination sites</td>
</tr>
<tr>
<td>135150</td>
<td>Birt-Hogg Dubé Syndrome</td>
<td>AD</td>
<td>HFH</td>
<td>17q11.2</td>
<td>BHD</td>
<td>folliculin</td>
<td>Unknown</td>
</tr>
<tr>
<td>132700</td>
<td>Cylindromatosis familial</td>
<td>AD</td>
<td>C</td>
<td>16q12-13</td>
<td>CYLD1</td>
<td>CYLD1</td>
<td>Tumour suppressor gene. Protein with 3 cytoskeletal-associated-protein-glycine-conserved domains implicated in the attachment of organelles to microtubules</td>
</tr>
</tbody>
</table>
Familial cutaneous melanoma

Definition
Familial melanoma is defined as the occurrence in at least two affected blood-relatives up to the third degree on one side of the family. This genetic susceptibility is caused germline mutations in the CDKN2A/p14ARF or CDK4 gene.

OMIM numbers

600160: Cyclin-dependant kinase inhibitor 2A; CDKN2A
Synonyms: CDK4 Inhibitor; multiple tumour suppressor 1, MTS1; TP16; p16(INK4); p16(INK4A); p14(ARF).

123829 Cyclin-dependant kinase 4; CDK4
Synonyms: Cell Division Kinase 4; Cutaneous malignant melanoma 3, CMM3.

155600 Melanoma, cutaneous malignant; CMM

Synonyms: Melanoma, malignant; Familial atypical mole-malignant melanoma syndrome, FAMMM; Melanoma familial, MLM; Dysplastic naevus syndrome, hereditary, DNS; Melanoma, cutaneous malignant 1, CMM1; B-K Mole syndrome.

155755 Melanoma-astrocytoma syndrome
Synonyms: Melanoma and neural system tumour syndrome

606719 Melanoma-pancreatic cancer syndrome
Synonyms: Familial atypical multiple mole melanoma pancreatic carcinoma syndrome (FAMMMPC)

Epidemiology
Cutaneous melanoma is a typical example of a multifactorial disease, where both genetic and environmental factors are involved and interact. Genetic factors were first suspected through the existence of familial aggregations of CM. The proportion of familial cases varies from 4-15% across different studies. Within large families, familial aggregation of melanoma was consistent with autosomal, dominant inheritance. In addition to CM family history, numerous epidemiological studies have demonstrated that cutaneous and pigmentary characteristics (the presence of numerous naevi, naevus atypia, skin colour, red hair and freckles), sun exposure (particularly during childhood) and reactions to sun exposure (inability to tan and propensity to develop sunburns) are major CM risk factors. Some melanoma risk factors also show familial aggregations independent of melanoma, suggesting the existence of genetic factors specific to these phenotypes (309). The various patterns of associations of these different phenotypes (phototype, naevus phenotypes and CM) across families are likely to result from complex interactions of genetic and environmental factors underlying these traits.

Clinical features and neoplastic disease spectrum
Cutaneous melanoma (CM)
Characteristics of familial melanoma include multiple cases of CM among blood-relatives on the same side of the family. Potential genetic predisposition may be suspected also in sporadic cases such as multiple primary CM in the same individual or early age of onset (1239).

Pancreatic cancer
The existence of an increased risk of pancreatic cancer in a subset of CDKN2A families has been reported (286,859).

Breast cancer
An excess of breast cancer has been described in two sets of families, Italian and Swedish (286,822).

Table 7.2: Inherited tumour syndromes

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>AR*</th>
<th>AD</th>
<th>BCC**</th>
<th>SCC</th>
<th>M M</th>
<th>M H</th>
<th>CSN</th>
<th>EC</th>
<th>M FA</th>
<th>CLA</th>
<th>M SL</th>
<th>FTK</th>
<th>ST</th>
<th>M M L</th>
<th>D</th>
<th>SSL</th>
<th>HFFH</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR* Autosomal Recessive</td>
<td>AD Autosomal Dominant</td>
<td>BCC** Basal Cell Carcinoma</td>
<td>SCC Squamous Cell Carcinoma</td>
<td>M M Malignant Melanoma</td>
<td>M H Multiple Hamartomatous</td>
<td>CSN Cutaneous Sebaceous Neoplasms</td>
<td>EC Epidermoid Cysts</td>
<td>M FA Multiple Facial Angiofibromas</td>
<td>CLA Cutaneous Lichen Amyloidosis</td>
<td>M SL Multiple Skin Lesions</td>
<td>FTK Fibromatous Tumours of the Skin</td>
<td>ST Skin Tumours</td>
<td>M M L Malignant Macules of the Lip</td>
<td>D Dermatosis</td>
<td>SSL Scleroderma-like Skin Changes</td>
<td>HFFH Hair Follicle Hamartomas</td>
<td>C Cyclindroma</td>
<td></td>
</tr>
<tr>
<td>a Already described in the WHO Classification of Tumours of the Digestive System (944)</td>
<td>b Already described in the WHO Classification of Tumours of Soft Tissue and Bone (756)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Fig. 7.1 Interaction of environmental (sun exposure) and genetic factors in the evolution of cutaneous melanoma (CM).

Fig. 7.2 Effect of great number of naevi (GNN), atypical naevi (AN) and sunburns (SB) on cutaneous melanoma (CM) risk in CDKN2A mutation carriers.
Inherited tumour syndromes

Nervous system tumours
Rare families have been described displaying melanoma and neural system tumours (NSTs) over several generations (129,1230). This has been termed melanoma-astrocytoma syndrome due to the presence of cerebral astrocytomas in the first family described.

Uveal melanoma (UM)
Certain melanoma-prone kindred have members affected by either uveal and/or cutaneous melanoma. The first CDKN2A germline mutation was detected recently in a melanoma-prone family, where one carrier was affected by UM and the other by CM (Kannengiesser C. et al., Gene Chromosome and Cancer, pending).

Naevus:
Naevus: total number (TN), clinically atypical (AN), histologically dysplastic (DN)
These naevus phenotypes are major risk factors for CM but whether they represent precursor lesions in the course of tumour development is still unclear. There are several lines of evidence suggesting that distinct genetic factors may be involved in CM and number of naevi (309). CDKN2A does not appear to be a “naevus” predisposing gene; this phenotype was found in only half of the subjects with a CDKN2A gene mutation and who had developed melanoma (2226) and a study of Australian twins has reported that a CDKN2A-linked gene may influence flat moles but has no effect on raised or atypical moles (2601). Naevus phenotypes (TN, AN and/or DN) have been shown to influence the penetrance of CDKN2A in melanoma-prone North-American and French families (860,452A) with a greater effect of DN in non-carriers than in carriers of CDKN2A mutations in the American sample.

Genetics
Gene structure and mutations
Two genes (encoding three proteins) conferring a high risk of developing melanoma have been identified to date, CDKN2A/p14ARF and CDK4. In addition, a low-risk melanoma susceptibility gene has also been identified, the melanocortin-1 receptor gene (MC1R).

CDKN2A/p16INK4A gene
Linkage analyses, cytogenetic studies and loss of heterozygosity (LOH) studies in tumour cells have led researchers to suspect the existence of a CM susceptibility gene at 9p21 locus. The gene, p16INK4A/CDKN2A, was cloned in 1993 (2140) and formally identified as a melanoma susceptibility gene in 1994 (1088,1184).

The CDKN2A transcript includes exons 1α, 2 and 3. It encodes the 156 amino-acid p16INK4A protein composed of four ankyrin repeats which are motifs involved in protein-protein interactions. P16INK4A binds to cyclin-dependent kinase 4 (CDK4) and 6 (CDK6), therefore preventing binding of cyclin D1 to the CDKs. Cyclin D1/CDK4/6 complexes participate in the phosphorylation of the retinoblastoma protein (RB), allowing the cell to progress beyond the G1 phase of the cell division cycle (2166). The p16INK4A protein inhibits RB-dependant cell cycle and therefore acts as a tumour suppressor.

The search for mutations of the CDKN2A gene in numerous familial studies around the world shows that the frequency of CDKN2A mutations is about 20% on average but varies from 5-50% depending on the criteria for family selection. Homozygotes for CDKN2A germline mutation have been described in relation to a Dutch founder effect; they display similar phenotypes than heterozygous individuals (912). Mutations of the CDKN2A gene are detected in approximately 10% of sporadic multiple melanoma cases, without any evidence of de novo mutations up to date but in relation to the existence of a founder effect for some of them (115). To date, no germ line mutations have been found in cases of childhood melanoma (<18-20 years of age) lacking a family CM context (2507). Most CDKN2A mutations are missense mutations scattered throughout the coding sequences of exons 1α and 2. Functional studies of mutant p16INK4A proteins have been carried out using several assays displaying various sensitivity: CDK-binding, kinase activity inhibition, growth arrest and protein cellular localisation assays. Two more complex mutations have been also described: a mutation located within CDKN2A 5’UTR, creating an aberrant initiation codon (1435) and a deep intronic mutation (IVS2-105A/G) of CDKN2A, leading to aberrant mRNA splicing (956). Recurrent mutations described in melanoma-prone families from different continents have been shown to be founder mutations (115,488).

Within the International Melanoma Consortium, CDKN2A mutation penetrance was estimated to be, in a set of 80...
families, 0.58 in Europe, 0.76 in the United States and 0.91 in Australia, by age 80 years [251]. This variation of penetrance by geographical location was found to be similar to the variation of overall population incidence rates among these countries. This suggests that the same risk factors mediate CM risk to the same extent in CDKN2A mutation carriers as in non-carriers. Moreover, CM risk does not change according to whether or not the mutation can simultaneously alter the p16INK4A and p14ARF proteins.

Three MC1R variant alleles also act as modifiers of melanoma risk in families segregating CDKN2A mutations: MC1Rvar/var genotypes increased the melanoma penetrance in CDKN2A carriers from 50-84% in Australia (sunny country) and from 18–55% in the Netherlands (less sunny country) [291,2410].

CDKN2A/p14ARF gene
In 1995, it was discovered that part of CDKN2A gene was common to another transcript. This second transcript (exons 1b, 2 and 3) encodes the human p14ARF protein (ARF meaning “alternative reading frame”) composed of 132 amino-acid, encoded by exons 1b and 2. According to the current state of knowledge, p14ARF is involved in regulation of the cell cycle and apoptosis via the p53 and RB pathways, by interacting with MDM2 (leading to p53 protein accumulation and to RB inactivation) and E2F1 proteins [1437].

Mutations in exon 2 potentially affect p16INK4A and p14ARF proteins at the same time. Despite this dual coding capacity of the INK4A/ARF locus, recent description of three p14ARF germ-line alterations involving only exon 1b suggests a direct role for p14ARF inactivation via the p53 and RB pathways, by interacting with MDM2 (leading to p53 protein accumulation and to RB inactivation) and E2F1 proteins [1437].

A role for both p14ARF and p16INK4A/CDKN2A genes?
Germ-line alterations presumably altering both p16INK4A and p14ARF functions, have been described in three CM and NSTs families: two large deletions involving the INK4A locus [128] and a CDKN2A splice point mutation, leading to p16INK4A and p14ARF transcripts lacking exon2 [1818]. However, it cannot be concluded that both p16INK4A and p14ARF inactivation are necessary for melanoma-astrocytoma syndrome as a fourth such family has been also described with a germ line deletion apparently restricted to the p14ARF - specific exon 1b [1890].

CDK4 gene
The CDK4 gene on chromosome 12q13 is composed of 8 exons within a 5-kilobases (kb) segment. The initiation codon is located in exon 2, the stop codon in exon 8. This gene encodes the cyclin-dependant kinase 4 (CDK4), a 304 amino-acid protein. It has been identified as a melanoma predisposing gene in three families world-wide [2226,2607]. Germline mutations affect Arg-24 residue in exon 2, which plays a key role in p16INK4A binding. The mutation induces the loss of the cell cycle down-regulation signal that p16INK4A exerts through RB phosphorylation. In a “knock-in” Cdk4R24C/R24C mouse model, constitutive Cdk4 activation is oncogenic [1891].

Application of genetic testing in the clinical testing
There is some evidence that non-carrier of CDKN2A mutations in melanoma-prone families may have a higher incidence of melanoma than the general population, presumably due to co-inheritance of other low-risk susceptibility genes and common environmental risk amongst family members. Therefore, genetic testing for melanoma is of limited clinical utility to date, mainly because a negative genetic test may give dangerously false security. Testing should be done in research protocols and first-degree relatives of high-risk individuals should be engaged in the same programs of melanoma prevention and surveillance, irrespective of the results of any gene testing. However, in countries of low melanoma incidence such as most European countries, DNA testing may improve compliance with sun protection and surveillance in identified mutation carriers. In such situations, CDKN2A testing could be proposed after careful genetic counselling [1238].
Inherited tumour syndromes

**Definition**
Xeroderma pigmentosum (XP) is an autosomal recessive disease with sun sensitivity, photophobia, early onset of freckling, and subsequent neoplastic changes on sun-exposed surfaces (284, 778). There is cellular hypersensitivity to UV radiation and to certain chemicals in association with abnormal DNA repair (2419). Some of the patients have progressive neurologic degeneration. The XP syndrome is genetically heterogeneous. Patients with defective DNA nucleotide excision repair (NER) have defects in one of 7 NER genes, while XP variant patients have normal NER and a defect in a polymerase gene (316,500).

**OMIM Numbers**
278700 - XPA
133510 - XPB
278720 - XPC
278730 - XPD
278740 - XPE
278760 - XPF
278780 - XPG
278750 - XP variant

**Synonyms**
De-Sanctis Cacchione syndrome, pigmented xeroderma, xeroderma pigmentosum variant

**Epidemiology**
**Incidence**
Xeroderma pigmentosum occurs with an estimated frequency of 1:1,000,000 in the United States (1322). It is more common in Japan, the Middle East and North-Africa. Patients have been reported worldwide in all races including Whites, Asians, Blacks, and Native Americans. Consanguinity is common. There is no significant difference between the sexes.

**Clinical features**
Abnormalities may be present in the skin, eyes, or nervous system. There is a greatly increased frequency of cancer on sun-exposed sites.

**Skin**
Approximately half of the patients with XP have a history of acute sunburn reaction on minimal UV exposure (1322). The other patients give a history of normal tanning without excessive burning. In all patients, numerous freckle-like hyperpigmented macules appear on sun-exposed skin.
The median age of onset of the cutaneous symptoms is between 1 and 2 years (1321). Repeated sun exposure results in dry and parchment-like skin with increased pigmentation, hence the name xeroderma pigmentosum (“dry pigmented skin”). Pre-malignant actinic keratoses may develop at an early age.

**Eyes**
Ocular abnormalities are almost as common as the cutaneous abnormalities (801,871,2424). Clinical findings are strikingly limited to the anterior, UV-exposed structures. Photophobia is often present and may be associated with prominent conjunctival injection. Continued UV exposure of the eye may result in severe keratitis leading to corneal opacification and vascularization. The lids may develop loss of lashes and atrophy of the skin of the lids results in the lids turning out (ectropion), or in (entropion), or complete loss of the lids in severe cases. Benign conjunctival inflammatory masses or papillomas of

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**Fig. 7.5** Xeroderma pigmentosum. A Face of a 16 year old patient showing dry skin with hyperpigmentation, atrophy and cheilitis. B Posterior view of the same patient showing absence of pigmented changes on areas protected from sunlight. C Face of a 14 year old patient showing freckle-like lesions with different amounts of pigmentation, an actinic keratoses, a basal cell carcinoma and a scar with telangiectasia at the site of removal of another neoplasm. D Xeroderma pigmentosum. Eye of the 22 year old patient showing secondary telangiectasia invading the cloudy cornea, and atrophy and loss of lashes of the lower lid. Figures from K.H. Kraemer (1319).
the lids may be present. Basal and squamous cell carcinoma, and melanoma of UV-exposed portions of the eye are common.

Nervous system
Neurologic abnormalities have been reported in approximately 30 percent of the patients. The onset may be early in infancy (the De-Sanctis Cacchione syndrome) or delayed until the second decade. The neurologic abnormalities may be mild (e.g., isolated hyporeflexia) or severe, with progressive mental retardation, sensorineural deafness (beginning with high-frequency hearing loss), spasticity, or seizures. In clinical practice, deep tendon reflex testing and routine audiometry can usually serve as a screen for the presence of XP-associated neurologic abnormalities. The predominant neuropathologic abnormality found at autopsy in patients with neurologic symptoms was loss (or absence) of neurons, particularly in the cerebrum and cerebellum (1894).

Cancer
Patients with XP under 20 years of age have a greater than 1000-fold increased risk of skin cancer (basal cell or squamous cell carcinoma or melanoma) (1321). Multiple primary skin cancers are common. The median age of onset of non-melanoma skin cancer reported in patients with XP was 8 years. This 50-year reduction in comparison to the general population is an indication of the importance of DNA repair in protection from skin cancer in normal individuals. There is a greatly increased frequency of cancer of the anterior portion of the eye and of the oral cavity, particularly squamous cell carcinoma of the tip of the tongue. These are presumed sun-exposed sites. Brain (sarcoma and medulloblastoma), central nervous system (astrocytoma of the spinal cord), lung, uterine, breast, pancreatic, gastric, renal, and testicular tumours and leukemias have been reported in a small number of XP patients. Overall, these reports suggest an approximate ten to twenty-fold increase in internal neoplasms (1321).

Diagnosis
There have been no consistent routine clinical laboratory abnormalities in patients with XP. Diagnosis is based on clinical features and confirmed by tests of cellular hypersensitivity to UV damage along with a defect in nucleotide excision repair for classical XP (778).

Cellular hypersensitivity
Cultured cells from patients with XP generally grow normally when not exposed to damaging agents. The population growth rate or single-cell colony-forming ability is reduced to a greater extent than normal, however, following exposure to UV radiation. A range of post-UV colony-forming abilities has been found with fibroblasts from patients, some having extremely low post-UV colony-forming ability and others having nearly normal survival. XP fibroblasts are also deficient in their ability to repair some UV-damaged viruses or plasmids to a functionally active state. XP variant cells are specifically sensitive killing by UV-irradiation in the presence of caffeine.

DNA repair
Cells from most XP patients have a defect in one of 7 genes (XPA through XPG) involved in the nucleotide excision repair (NER) system (500). The NER pathway is described in Figure 7.6 (2253). The DNA repair defect can be measured by post-UV unscheduled DNA synthesis. Host cell reactivation assays can be used to determine the complementation group by use of a panel of cloned DNA repair genes. Cells from XP variant patients have normal NER but have a defect in an error-prone polymerase (pol eta) (316). Prenatal diagnosis can be performed by use of unscheduled DNA synthesis assays on cultured amniotic fluid cells and by molecular analysis of trophoblast biopsies (52,1309). Most XP cells have a normal response to treatment with x-rays, indicating the specificity of the DNA repair defect.

Genetics
The seven complementation groups found for the classical XP correspond to
seven genes involved in NER (2253, 2419); XPC, XPE and XPA code for proteins able to recognize DNA lesions produced by various DNA damaging agents, including UV-radiation. XPB and XPD are two helicases necessary to open the double helix at the site of the lesion. XPF and XPG are two endonucleases able to cut the damaged strand at the 5' and 3' sites, respectively. Numerous other enzymes are necessary to complete the error-free repair but defects have not yet been identified in these genes in association with human diseases.

There is marked clinical and molecular heterogeneity in XP. Patients in XP complementation groups A, B, D, and G may have neurological abnormalities in addition to skin involvement. Patients with defects in XP complementation group D may have one of at least 5 different clinical phenotypes: XP with skin disease, XP with neurological disease, the XP/Cockayne syndrome complex (1894), trichothiodystrophy (TTD - a disorder with sulphur deficient brittle hair) (1113) or XP/TTD (315).

**Treatment**

Management of patients with XP is based on early diagnosis, life-long protection from UV radiation exposure, and early detection and treatment of neoplasms (778).
Naevoid basal cell carcinoma (Gorlin) syndrome

Definition
The naevoid basal cell carcinoma syndrome (NBCCS) is a genodermatosis caused by germline mutations of the PTCH gene. It is characterized by numerous basal cell cancers and epidermal cysts of skin, odontogenic keratocysts of jaws, palmar and plantar pits, calcified dural folds, various neoplasms or hamartomas (ovarian fibromas, medulloblastoma, lymphomesenteric cysts, fetal rhabdomyomas, etc.) and various stigmata of maldevelopment (rib and vertebral abnormalities, Sprengel anomaly, enlarged head circumference, cleft lip and/or palate, cortical defects of bones and other lesions.

OMIM number 109400

Synonyms
Naevoid basal cell carcinoma syndrome, Gorlin syndrome, Gorlin-Goltz syndrome, basal cell naevus syndrome.

Epidemiology
The frequency of NBCCS has been variously estimated. It constitutes about 0.4% of all cases of basal cell carcinomas. Evans et al (698) suggested that the minimal prevalence was 1 per 57,000.

Clinical features
Although the syndrome is remarkably variable in sites of involvement, the most persistent problems are the odontogenic keratocysts and the inordinate number of basal cell carcinomas, only a fraction of which become aggressive (867, 868, 1273).

Skull
The head appears large (>60 cm in adults). Relative macrocephaly (occipitofrontal circumference greater than 95th centile for height) is found in 50%. Mild mandibular prognathism, noted as “pouting lower lip”, is seen in 35%.

Basal cell carcinomas
These may appear as early as 2 years of age, especially on the nape, most often proliferate between puberty and 35 years. There appears to be a relationship to increased sun exposure. The basal cell cancers, which vary in number from a few to literally thousands, range in size from 1-10 mm in diameter. They are pearly to flesh coloured to pale brown and may be mistaken for skin tags or naevi. The basal cell carcinomas which most often involve the face and upper chest may become aggressive and invade locally. Increase in size, ulceration, bleeding and crusting indicate invasion. Radiation therapy causes proliferation of basal cell carcinomas and invasion several years later.

Milia
Small keratin-filled cysts (milia) are found intermixed with basal cell carcinomas in 30-50%. Larger, often multiple, epidermal cysts arise on the limbs and trunk in about 35-50% of whites. Multiple cysts are located on the palpebral conjunctiva in about 40%.

Pits
Palmar and, somewhat less often, plantar
Inherited tumour syndromes

pits (1-2 mm) are asymmetrically present in 65-80%.

Keratocystic odontogenic tumours
Characteristically, multiple (average-6; range 1-30) odontogenic keratocysts, now termed keratocystic odontogenic tumours (153), of both the upper and more often lower jaws appear after the seventh year of life with an overall frequency of 65%. They effect marked tooth displacement but only rarely cause fracture. There is marked tendency (over 60%) for these cysts to recur following surgery.

Medulloblastoma
This embryonal neoplasm is present in 3-5% of NBCCS patients and characteristically presents during the first 2 years of life as opposed to 7-8 years in the general population (698). Because medulloblastoma presents early (mean 2.5 years) in patients with NBCCS, children who present with the tumour, especially those less than 5 years, should be carefully examined for signs of the syndrome.

Radiation therapy of medulloblastoma results in extreme numbers of invasive basal cell carcinomas appearing in the radiation field (from nape to base of spine).

Fibromas
Cardiac fibromas occur in 3% (698). Conversely, about 5% of patients with cardiac fibromas have NBCCS. Presentation time has varied from birth to 60 years. Most have been found incidentally. Ovarian fibromas are noted in 25% (698). The ovarian fibromas associated with NBCCS are most often bilateral (75%). Minor kidney anomalies and hypogonadotropic hypogonadism are found in roughly 5%. Gorlin (868) reviewed examples of fetal rhabdomyoma.

Imaging
Lamellar calcification of the falx cerebri is found in 55-95% (normal-5%). Calcification of the tentorium cerebelli has been noted in 20-40%, the petroclinoid ligament in 20%, and the diaphragma sellae in 60-80%. Radiographically, this appears as if the sella turcica is bridged, i.e., as if there were fusion of the anterior and posterior clinoid processes (1897,1898). Odontogenic keratocysts first appear at about 7-8 years of age and increase in number from puberty onward. They peak during the second and third decades. The cysts cause marked tooth displacement. They may invade the paranasal sinuses and, in the mandible, may extend from the molar-ramus area to the coronoid processes. Fused, splayed, hypoplastic or bifid ribs have been documented in 45-60%. Kyphoscoliosis with or without pectus is found in 25-40% with spina bifida occulta of the cervical or thoracic vertebrae in 60%. Sprengel deformity and/or unusual narrow sloping shoulders have been described in 10-40%. Other anomalies seen in about 40% include cervical or upper thoracic vertebral fusion, hemivertebra, and lumbarization of the sacrum. Pectus occurs in about 15-25% (1897,1898).

Small pseudocystic bone lesions (flame-shaped luencies) have been identified in the phalanges, metapodial bones, carpal and tarsal bones, long bones, pelvis and calvaria in 30%. Calvarial

Table 7.3
Diagnostic findings in adults with naevoid basal cell carcinoma syndrome.
Modified, from R.J. Gorlin (868).

<table>
<thead>
<tr>
<th>50% or greater frequency</th>
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<tbody>
<tr>
<td>Enlarged occipitofrontal circumference</td>
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<tr>
<td>(macrocephaly, frontal-parietal bossing)</td>
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<tr>
<td>Multiple basal cell carcinomas</td>
</tr>
<tr>
<td>Odontogenic keratocysts of jaws</td>
</tr>
<tr>
<td>Epidermal cysts of skin</td>
</tr>
<tr>
<td>High-arched palate</td>
</tr>
<tr>
<td>Palmar and/or plantar pits</td>
</tr>
<tr>
<td>Rib anomalies (splayed, fused, partially missing, bifid, etc.)</td>
</tr>
<tr>
<td>Spina bifida occulta of cervical or thoracic vertebrae</td>
</tr>
<tr>
<td>Calcified falx cerebri</td>
</tr>
<tr>
<td>Calcified diaphragma sellae (bridged sella, fused clinoids)</td>
</tr>
<tr>
<td>Hyperpneumatization of paranasal sinuses</td>
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<table>
<thead>
<tr>
<th>49-15% frequency</th>
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<tbody>
<tr>
<td>Brain ventricle asymmetry</td>
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<tr>
<td>Calcification of tentorium cerebelli and petroclinoid ligament</td>
</tr>
<tr>
<td>Calcified ovarian fibromas</td>
</tr>
<tr>
<td>Short fourth metacarpals</td>
</tr>
<tr>
<td>Kyphoscoliosis or other vertebral anomalies</td>
</tr>
<tr>
<td>Lumbarization of sacrum</td>
</tr>
<tr>
<td>Narrow sloping shoulders</td>
</tr>
<tr>
<td>Prognathism</td>
</tr>
<tr>
<td>Pectus excavatum or carinatum</td>
</tr>
<tr>
<td>Pseudocystic lytic lesion of bones (hamartomas)</td>
</tr>
<tr>
<td>Strabismus (exotropia)</td>
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<tr>
<td>Syndactyly</td>
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<td>Synophrys</td>
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</table>

<table>
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<tr>
<th>14% or less but not random</th>
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<tbody>
<tr>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>True ocular hypertelorism</td>
</tr>
<tr>
<td>Meningioma</td>
</tr>
<tr>
<td>Lymphomesenteric cysts</td>
</tr>
<tr>
<td>Cardiac fibromas</td>
</tr>
<tr>
<td>Fetal rhabdomyoma</td>
</tr>
<tr>
<td>Ovarian fibrosarcoma</td>
</tr>
<tr>
<td>Marfanoid build</td>
</tr>
<tr>
<td>Anosmia</td>
</tr>
<tr>
<td>Agenesia of corpus callosum</td>
</tr>
<tr>
<td>Cyst of septum pellucidum</td>
</tr>
<tr>
<td>Cleft lip and/or palate</td>
</tr>
<tr>
<td>Low-pitched female voice</td>
</tr>
<tr>
<td>Polydactyly, postaxial - hands or feet</td>
</tr>
<tr>
<td>Sprengel deformity of scapula</td>
</tr>
<tr>
<td>Vertebral body fusion</td>
</tr>
<tr>
<td>Congenital cataract, glaucoma, coloboma of iris, retina, optic nerve, medullated retinal nerve fibers</td>
</tr>
<tr>
<td>Subcutaneous calcifications of skin (possibly underestimated frequency)</td>
</tr>
<tr>
<td>Minor kidney malformations</td>
</tr>
<tr>
<td>Hypogonadism in males</td>
</tr>
<tr>
<td>Mental retardation</td>
</tr>
</tbody>
</table>

Table 7.4
Diagnostic criteria for NBCCS
Diagnosis based on two major or one major and two minor criteria.

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
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<tbody>
<tr>
<td>1. More than 5 BCCs or one under age of 20 yrs</td>
</tr>
<tr>
<td>2. Odontogenic keratocyst</td>
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<tr>
<td>3. Three or more palmar pits</td>
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<tr>
<td>4. Bilamellar calcification of falx cerebri</td>
</tr>
<tr>
<td>5. Bifid, fused or splayed ribs</td>
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<tr>
<td>6. First degree relative with NBCCS</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Macrocephaly adjusted for height</td>
</tr>
<tr>
<td>2. Frontal bossing, cleft lip/palate, hypertelorism</td>
</tr>
<tr>
<td>3. Sprengel deformity, pectus, syndactyly of digits</td>
</tr>
<tr>
<td>4. Bridging of sella turcica, hemivertebrae, flame-shaped radiolucencies</td>
</tr>
<tr>
<td>5. Ovarian fibroma</td>
</tr>
<tr>
<td>6. Medulloblastoma</td>
</tr>
</tbody>
</table>

Based on V.E. Kimonis et al (1273).
involvement may give the impression that medulloblastoma has spread to bone. Histologically, the flame-like lesions are hamartomas consisting of fibrous connective tissue, nerves and blood vessels. Subcutaneous calcification of fingers and scalp has been rare. Sclerotic bone lesions have been reported occasionally. Ovarian fibromas are found in about 25% of females. They are bilateral and often calcified, at times overlapping medially. Prenatal diagnosis by sonography has been accomplished (235).

**Genetics**

The first link between the SONIC HEDGEHOG (SHH) signalling pathway and tumour formation in humans was in familial cancers, as 30-40% of NBCCS patients harbour loss-of-function mutations in the PATCHED1 (PTCH1) gene (514,939,1992). That disruption of the SHH signalling pathway is a major determinant of tumour formation, particularly for BCCs, was established from the discovery that PTCH1 is mutated in 10-38% of sporadic BCCs (514,1992). Inactivation of both PTCH1 alleles also results in the formation of cysts (1408). Consistent with its pivotal role in embryonic development, aberrant SHH signalling is associated with a range of human developmental anomalies (2434). In NBCCS, tumours (BCCs, keratoceysts, meningiomas, ovarian fibromas, odontogenic keratocysts) exhibit loss of heterozygosity (LOH) in the PTCH1 locus (9q22.3) (514). Various physical anomalies (bifid rib, macrocephaly, cleft lip, etc.) apparently need but one-hit (1407). LOH in the PTCH1 locus was observed in 89% of hereditary BCCs. The majority (61-71%) of germline PTCH1 mutations are rearrangements. Most mutations (>80%) are likely to represent null mutations since they are predicted to result in truncation of the PTCH1 protein (133, 514,1408,1992).

The PTCH1 tumour suppressor gene comprises 23 exons which encode 12 putative transmembrane domains and two large extracellular loops. The function of PTCH1 is to silence the SHH signalling pathway in absence of active SHH ligand (2308). In presence of SHH, the pathway acts in at least two ways to regulate target genes. One is to activate GLI 1/2 transcription factors and the other is to inhibit the formation of GLI repressors, mostly from GLI3, to derepress target genes (1992).

**Prognosis and predictive factors**

New keratocystic odontogenic tumours (odontogenic keratocysts) and basal cell carcinomas continue for life. Limitation of sun exposure reduces the appearance of the skin cancers. The medulloblastoma appears before the age of 4 years, the ovarian fibromas after puberty. Therapeutic radiation should be avoided whenever possible due to the high occurrence of basal cell carcinomas in the radiation field.
Cowden syndrome

Definition
Cowden syndrome (CS) is an autosomal-dominant disorder with age-related penetrance and variable expression, characterized by multiple hamartomas arising in tissues derived from all three embryonic germ cell layers and with a high risk of developing benign and malignant neoplasms in many organ systems, especially in the skin, breast, and thyroid gland. The condition was described in 1963 by Lloyd and Dennis (1439). It is caused by germline mutations in the tumour suppressor gene PTEN located on chromosome 10q23 (1424).

OMIM number 158350

Synonyms
Multiple hamartoma syndrome, Cowden disease

Epidemiology
Incidence
The incidence of CS, after PTEN was identified as the gene, was found to be 1 in 200 000 (1693). The latter may be an underestimate, since CS has variable expression and often manifests itself only with subtle skin changes, so that this condition may be difficult to recognize (688). Although the exact proportion of isolated and familial cases is not known, previous and on-going observations suggest that 40-60% are familial (1521, 2448,688A).

Clinical features
CS is classically characterized as a multiple hamartoma syndrome with a high risk of breast and thyroid cancers. Although the reported age at onset varies from 4–75 years (1451), CS usually manifests in the second or third decade. More than 90% of individuals affected with CS are likely to manifest a phenotype by the age of 20 years, and 99% develop at least mucocutaneous lesions by the age of 30 years (1694,2448). CS is characterized by the development of hamartomas, benign and malignant tumours in multiple organ systems including the skin, soft tissues, breast, thyroid gland, gastrointestinal tract, genitourinary tract, and central nervous system. The most common lesions are trichilemmomas (90-100%), breast fibroadenomas (70%), thyroid adenomas (40-60%), multinodular goiter (40–60%), and multiple gastrointestinal polyps (35–40%) (688,1451). Macrocephaly is seen in 35-40% of cases. Malignant neoplasms develop in the breast in 25–50% of CS females, in the thyroid gland in 3–10% (usually follicular adenocarcinoma) and in the uterus in 3-6%. The most common malignant neoplasm in the breast is ductal adenocarcinoma, which is bilateral in one third of cases (2098). The average age of CS patients at diagnosis of breast cancer is 10 years younger than in those with sporadic disease (2252). Male breast cancers also occur, but with unknown frequency (704,1519). A feature that distinguishes CS from other breast cancer susceptibility syndromes is the occurrence of benign breast disease prior to the development of breast cancer (2098,2099).

Many other internal malignancies have been reported to occur in individuals affected with CS. There are no data to state whether they are true components of this syndrome or merely coincidental.

Bannayan–Riley–Ruvalcaba syndrome (BRRS)
This pediatric disorder characterized by congenital macrocephaly, multiple lipomatosis and angiomatosis involving the skin and visceral tissues, intestinal hamartomatous polyposis, and pigmented penile lesions, shows a partial clinical overlap with CS (711,1519).

Diagnostic criteria
The International Cowden Consortium originally proposed a set of operational diagnostic criteria in 1996 (1694). Because of new data, the Consortium revised the criteria in 2000 (688), which...
Cutaneous and mucosal lesions
Cutaneous lesions are the most important hallmarks for CS, since they are present in almost every patient and frequently appear prior to the development of any internal disease (1030). Facial papules are the most frequent lesions (85-90%). They are mainly located in periorificial regions, sometimes extending into the nostrils. Histopathologically, the papules frequently show non-specific verrucous acanthomas, trichilemmomas, perifollicular fibromas or may reveal lesions with features intermediate between trichilemmomas, inverted follicular lesions with features intermediate perifollicular fibromas or may reveal verrucous acanthomas, trichilemmomas, and tumour of follicular infundibulum {322,2249-2251}. Although human papilloma virus has not been consistently found in these lesions, some experts believe that trichilemmomas in CS represent verrucae vulgaris with trichilemmal differentiation (28). Acral verrucous hyperkeratosis on the extensor sides of the extremities and palmoplantar translucent keratoses are seen in approximately 20-30% of cases. Histopathologically, they show wart-like changes, with prominent compact orthokeratosis, hypergranulosis, and acanthosis, in some cases with trichilemmal differentiation. Involvement of the oral mucosa is present in over 80% of cases. Coalescent lesions produce the characteristic cobblestone-like pattern in 40% of patients. Histopathologically, these lesions are composed of acellular collagen fibres, with a predominantly whorl-like arrangement (2251). Mucosal papules and nodules with trichilemmoma-like histopathological features are also common. A scrotal tongue is another common finding. Usually mucocutaneous lesions are present in multiple locations, and extension to the oropharynx, larynx, tongue, and nasal mucosa may occur.

Other cutaneous lesions reported to occur in individuals affected with CS include lipoma, angiolipoma, multiple sclerotic fibromas, squamous cell carcinoma, melanoma, basal cell carcinoma, Merkel cell carcinoma, haemangiomas, xanthoma, vitiligo, neuroma, apocrine hidrocystoma, café au lait spots, periorificial and acral lentigines and acanthosis nigricans (reviewed in (748,1030))

Table 7.5

<table>
<thead>
<tr>
<th>Pathognomonic criteria</th>
<th>Mucocutaneous lesions</th>
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<tbody>
<tr>
<td></td>
<td>Trichilemmomas, facial</td>
</tr>
<tr>
<td></td>
<td>Acral keratoses</td>
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<tr>
<td></td>
<td>Papillomatous papules</td>
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<tr>
<td></td>
<td>Mucosal lesions</td>
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<table>
<thead>
<tr>
<th>Major criteria</th>
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<tbody>
<tr>
<td>Breast carcinoma</td>
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<tr>
<td>Thyroid carcinoma (nonmedullary), especially follicular thyroid carcinoma</td>
</tr>
<tr>
<td>Macrocephaly (megalencephaly) (~95th percentile or more)</td>
</tr>
<tr>
<td>Lhermitte-Duclos disease</td>
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<tr>
<td>Endometrial carcinoma</td>
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<tr>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Other thyroid lesions (eg, adenoma or multinodular goitre)</td>
</tr>
<tr>
<td>Mental retardation (IQ~75 or less)</td>
</tr>
<tr>
<td>Gastrointestinal hamartomas</td>
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<tr>
<td>Fibrocystic disease of the breast</td>
</tr>
<tr>
<td>Lipomas</td>
</tr>
<tr>
<td>Fibromas</td>
</tr>
<tr>
<td>Genitourinary tumours (eg, renal cell carcinoma, uterine fibroids) or malformation</td>
</tr>
</tbody>
</table>

**Operational diagnosis in an individual**
1. Mucocutaneous lesions alone if there are:
   1. (a) 6 or more facial papules, of which 3 or more are trichilemmoma, or
   2. (b) cutaneous facial papules and oral mucosal papillomatosis, or
   3. (c) oral mucosal papillomatosis and acral keratoses, or
   4. (d) 6 or more palmoplantar keratoses,
2. Two major criteria, one of which is macrocephaly or Lhermitte-Duclos disease
3. One major and three minor criteria
4. Four minor criteria

**Operational diagnosis in a family where one individual is diagnosed with Cowden syndrome**
1. The pathognomonic criterion or criteria
2. Any one major criterion with or without minor criteria
3. Two minor criteria

**Genetics**
PTEN/MMAC1/TEP1 on 10q23.3, is the susceptibility gene for CS (1424,1694).

**Gene structure and function**
PTEN comprises 9 exons spanning 120-150 kb of genomic distance. It encodes a 1.2 kb transcript and a 403 amino acid lipid dual-specificity phosphatase (it dephosphorylates both protein and lipid substrates) {1419,1421,2255,2448}. A classic phosphatase core motif is encoded within exon 5, which is the largest exon, constituting 20% of the coding region {1419,1421,1519,2256}. PTEN is the major 3-phosphatase acting in the phosphatidylinositol-3-kinase (PI3K)/Akt pathway {1478,2241}. To date, virtually all naturally occurring missense mutations tested abrogate both lipid and protein phosphatase activity, and one mutant, G129E, affects only lipid phosphatase activity. Overexpression of PTEN results, for the most part, in phosphatase-dependent cell cycle arrest at G1 and/or apoptosis, depending on cell type (reviewed in (687,2448)). There is also growing evidence that PTEN can mediate growth arrest independent of the PI3K/Akt pathway and perhaps independent of the lipid phosphatase activity {460,1564,2448,2495,2496}.

**Mutation spectrum**
Approximately 70-85% of CS cases, as strictly defined by the Consortium Criteria, have a germline PTEN mutation {1424,1519,2599}. If the diagnostic criteria are relaxed, then mutation frequencies drop to 10-50% {1464,1695,2382}. A
formal study which ascertained 64 unrelated CS-like cases revealed a mutation frequency of 2% if the criteria are not met, even if the diagnosis is made short of one criterion (1519). A single research centre study involving 37 unrelated CS families, ascertained according to the strict diagnostic criteria of the Consortium, revealed a mutation frequency of 80% (1519). As with most other tumour suppressor genes, the mutations found in \textit{PTEN} are scattered throughout all 9 exons. They comprise loss-of-function mutations including missense, nonsense, frame-shift and splice-site mutations (1519, 1521,2448). Approximately 30-40% of germline \textit{PTEN} mutations are found in exon 5. Further, approximately 65% of all mutations can be found in one of exons 5, 7 or 8 (1519,1521).

Although \textit{PTEN} is the major susceptibility gene for CS, one CS family, without \textit{PTEN} mutations, was found to have a germline mutation in the bone morphogenic protein receptor type 1A gene (\textit{BMPR1A}, MIM 601299), which is one of the susceptibility genes for juvenile polyposis syndrome (1066,2600). Whether \textit{BMPR1A} is a minor CS susceptibility gene or whether this family with CS features actually has occult juvenile polyposis is yet unknown.

Genotype-phenotype associations
Clinically useful genotype–phenotype correlations are being intensively investigated. Exploratory genotype-phenotype analyses revealed that the presence of a germline mutation was associated with a familial risk of developing a malignant breast disease. Further, missense muta-

...
Carney complex

Definition
Carney complex (CNC) is a lentiginosis-multiple endocrine neoplasia syndrome caused by at least two distinct mutations and characterized by multiple often unique tumours including myxomas and schwannomas, endocrine abnormalities, and cutaneous pigmentary lesions (397).

OMIM numbers
CNC1 160980; CNC2 605244

Synonyms
NAME syndrome (111), LAMB syndrome (1926).

Epidemiology
Carney complex is an uncommon disorder, inherited in an autosomal dominant fashion. More than 350 cases are known involving more than 65 families. The penetrance is high but the expressivity is highly variable. Patients may present with cutaneous, cardiac, or endocrine lesions; often the diagnosis is delayed until multiple manifestations are present.

Localization
The most commonly involved organs are the skin (75%), heart (50%) and adrenal glands (25%).

Clinical features
The cutaneous findings in CNC are often most dramatic. Patients may have multiple flat pigmented lesions that have been described both as ephelides (freckles) with an increased amount of melanin (111) and as lentigines with an increased number of melanocytes (1926). Blue naevi are another marker of the syndrome; many exhibit epithelioid features on microscopic examination (396). Pigmented lesions are also common on mucosal surfaces, such as the lips, mouth, conjunctiva and genital mucosa (1244). Some patients have no pigmentary changes. Another highly specific cutaneous finding is myxomas, especially when they affect the eyelids and the external ear canal (734). Histologically, these benign tumours often feature strands of lacy epithelium (398). The most dramatic systemic finding is cardiac myxoma(s). The CNC-associated myxomas have important differences from sporadic cardiac myxomas; they are more likely to be familial, multiple, occur at a younger age, involve the ventricles and recur (2433). Recurrent cardiac myxoma(s) may require multiple surgical resections that may result in postoperative arrhythmias and increased mortality.

The most common endocrine finding is primary pigmented nodular adrenal disease, a very rare ACTH-independent cause of Cushing syndrome (25%) (2164). The adrenal glands show bilateral, pigmented nodules with internodular cortical atrophy (881,2571). One of Cushing’s first patients, Minnie G., may well have had CNC (395). Acromegaly and thyroid tumours (2275) are each seen in around 10% of patients. About one-third of male patients have large-cell calcifying Sertoli cell tumours of the testes, often bilateral and sometimes leading to precocious puberty (1734).

Two other uncommon tumours which should suggest the presence of CNC are psammomatous melanotic schwannomas (20%) of the GI tract, sympathetic chain and skin (394), and myxoid mammary fibroadenomas (25% of women) (400).

Diagnostic procedures
Both epithelioid blue naevi and myxomas (the latter sometimes with a characteristic epithelial component) may be identified on skin biopsies and suggest the diagnosis of CNC. When investigation for Cushing syndrome reveals low or undetectable ACTH levels and no adrenal tumour, a diagnosis of primary pigment-
Inherited tumour syndromes should be considered and the patient evaluated for CNC, particularly if the patient is young or has multiple pigmented skin spots or lumps. Echocardiography is particularly important (2276).

**Differential diagnosis**
When multiple pigmented lesions are present, LEOPARD syndrome should be considered but myxomas are absent in this condition and the systemic manifestations more protean. Mucosal pigmentation strongly resembles that of Peutz-Jeghers syndrome, but intestinal polyps are not part of the usual spectrum of Carney complex.

**Genetics**
Carney complex is inherited in an autosomal dominant fashion. The gene for CNC1, known as *PRKAR1A*, normally encodes the protein kinase A regulatory subunit R1a (408,1284). When the mutated gene is present, the regulatory subunit is no longer produced. The patients are heterozygous for the mutation: the tumours tend to have LOH of the wild type allele for this regulatory gene. The *CNC2* gene is less well characterized but appears to be involved in regulating genomic stability, perhaps via the telomeres.

**Prognosis and predictive factors**
The prognosis depends on detecting cardiac myxoma, the most serious complex of CNC. The average age of 22 patients who died as the result of cardiac causes (cardiac failure from myxoma, cardiac myxoma emboli or cardiac arrhythmia) was 31 years. Timely diagnosis of the neoplasms requires an awareness of the possible significance of the pigmented skin spots, skin tumours, primary pigmented nodular adrenal disease and psammomatous melanotic schwannoma. Patients with lesions suggestive of CNC should be advised to have a general medical evaluation and an echocardiogram. Primary relatives of CNC patients should be similarly advised.

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**Fig. 7.15** A Eyelid myxoma in a young man with CNC and no cutaneous pigmentary changes. B Microscopic view of the same lesion, showing lacy epithelial strands amidst deposits of mucin.
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