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 TP53 tumour suppressor gene. Other genes involved in the multistep formation of skin cancer include PTCH and the 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

<table>
<thead>
<tr>
<th>Keratinocytic tumours</th>
<th>WHO code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td>8090/3</td>
<td>Actinic keratosis</td>
</tr>
<tr>
<td>Superficial basal cell carcinoma</td>
<td>8091/3</td>
<td>Arsenical keratosis</td>
</tr>
<tr>
<td>Nodular (solid) basal cell carcinoma</td>
<td>8097/3</td>
<td>PUVA keratosis</td>
</tr>
<tr>
<td>Micronodular basal cell carcinoma</td>
<td>8090/3</td>
<td>Verruca</td>
</tr>
<tr>
<td>Infiltrating basal cell carcinoma</td>
<td>8092/3</td>
<td>Verruca vulgaris</td>
</tr>
<tr>
<td>Fibroepithelial basal cell carcinoma</td>
<td>8093/3</td>
<td>Verruca planaris</td>
</tr>
<tr>
<td>Basal cell carcinoma with adnexal differentiation</td>
<td>8098/3</td>
<td>Verruca plana</td>
</tr>
<tr>
<td>Basosquamous carcinoma</td>
<td>8094/3</td>
<td></td>
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<tr>
<td>Keratotic basal cell carcinoma</td>
<td>8090/3</td>
<td>Acanthomas</td>
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<td>Squamous cell carcinoma</td>
<td>8070/3</td>
<td>Epidermolytic acanthoma</td>
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<td>Acantholytic squamous cell carcinoma</td>
<td>8075/3</td>
<td>Warty dyskeratoma</td>
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<td>Spindle-cell squamous cell carcinoma</td>
<td>8074/3</td>
<td>Acantholytic acanthoma</td>
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<td>Verrucous squamous cell carcinoma</td>
<td>8051/3</td>
<td>Lentigo simplex</td>
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<tr>
<td>Pseudovascular squamous cell carcinoma</td>
<td>8075/3</td>
<td>Seborrhoic keratosis</td>
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<tr>
<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
<td>Melanoacanthoma</td>
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<tr>
<td>Bowen disease</td>
<td>8081/2</td>
<td>Clear cell acanthoma</td>
</tr>
<tr>
<td>Bowenoid papulosis</td>
<td>8081/2</td>
<td>Large cell acanthoma</td>
</tr>
</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).

TNM classification of skin carcinomas

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>M - Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T - Primary tumour</td>
<td>M X: Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>TX: Primary tumour cannot be assessed</td>
<td>M 0: No distant metastasis</td>
</tr>
<tr>
<td>T0: No evidence of primary tumour</td>
<td>M 1: Distant metastasis</td>
</tr>
<tr>
<td>Tis: Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>T1: Tumour 2 cm or less in greatest dimension</td>
<td>Stage 0: Tis</td>
</tr>
<tr>
<td>T2: Tumour more than 2 cm but no more than 5 cm in greatest dimension</td>
<td>Stage I: T1</td>
</tr>
<tr>
<td>T3: Tumour more than 5 cm in greatest dimension</td>
<td>Stage II: T2, T3</td>
</tr>
<tr>
<td>T4: Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone</td>
<td>Stage III: T4</td>
</tr>
<tr>
<td>Stage IV: Any T</td>
<td>Stage IV: Any T</td>
</tr>
</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).
Keratinocytic tumours: Introduction

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 keratosis 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-nitosoguanidine), 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 epidermis. 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 (2483). 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 SMOOTHEMED 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-
ceous areas. Some examples of mor-
phoeic or sclerotic basal cell carcinoma
may resemble desmoplastic trichoep-
ithelioma or microcystic adnexal carcino-
ma 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 involve-
ment and excision margins particularly if
less than 1 mm. Although the majority of
basal cell carcinomas can be classified
into the nodular, micronodular, superfi-
cial, sclerosing/morphoeic or infiltrative
subtypes, it is not unusual to have a
mixed pattern.

**Immunoprofile**
Occasionally in curette specimens, dif-
ferentiation 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 car-
cinoma from squamous cell carcinomas
(2334). CK20, a marker for Merkel cells,
has been used to differentiate some
forms of trichoblastoma, trichoepithe-
loma 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 inva-
sive 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 meas-
ure more than 10 cm in diameter and
have been described as giant basal cell
carcinomas (1502,2009). Multiple recur-
rences 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, morphoeic and micron-
odular 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/morphoeic pat-
terns 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 difficul-
ty 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 compli-
cations of CNS extension (317,946).
Distance to the closest resection margin
is an important predictor of BCC recur-
rence (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
diameter. A fine pearly border or cen-
tral superficial erosions with a history of
contact bleeding may be present. Areas
of regression may appear as pale patch-
es or fibrosis. This variant makes up 10-
30% of basal cell carcinomas and occurs
most frequently on the trunk.

**Histopathology**
The histopathology consists of superfi-
cial lobules of basaloïd cells which proj-
et from the epidermis or from the sides
of follicles or eccrine ducts into the der-
mis and are surrounded by loose myxoid
stroma. The lobules are usually confined

![Fig. 1.3 Nodular BCC. Cribriform nodular basal cell carcinoma.](image1)

![Fig. 1.4 Nodular BCC with monster giant cells.](image2)
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 small nodules that permeate the dermis (1010). Individual nodules may appear to be separated by normal collagen. The tumour nodules may approximate the size of follicular bulbs and form subtle extensions into deep tissue. In contrast to nodular basal cell carcinoma the surgical margins of micronodular basal cell carcinoma may be underestimated. Perineural extension may be seen.

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Fig. 1.5 A Infiltrative basal cell carcinoma. B Mixed nodular and infiltrative basal cell carcinoma.

Fig. 1.6 Nodular cystic BCC A There are well circumscribed cystic nodules of atypical basaloid cells pushing into the deep dermis in a nodular pattern. B High power view of nodulocystic basal cell carcinoma showing cribriform cystic spaces filled with stromal mucin.
**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/morphoneic 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.

**Fig. 1.7** Fibroepithelial basal cell carcinoma (fibroepithelioma of Pinkus).

**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.

**Histogenisis**
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).

**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.

**Fig. 1.8** BCC with adnexal differentiation; basaloid follicular hamartoma.
Keratinocytic tumours

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.

Basosquamous carcinoma

Definition
Basosquamous carcinoma is a term used to describe basal cell carcinomas that are associated with squamous differentiation.

ICD-O code 8094/3

Synonyms
Metatypical carcinoma, basosquamous cell carcinoma

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.

Basal cell carcinoma with adnexal differentiation

Histopathology
This variant is characterized by adnexal differentiation in a BCC. 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.

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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.

ICD-O code 8094/3

Synonyms
Metatypical carcinoma, basosquamous cell carcinoma

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.

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Basal cell carcinoma with adnexal differentiation

Histopathology
This variant is characterized by adnexal differentiation in a BCC. 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.

ICD-O code 8094/3

Synonyms
Metatypical carcinoma, basosquamous cell carcinoma

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.

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**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 pilomatrixical 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 basaloid 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 pro-collagen 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 basaloid 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 (680) 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), pigmented (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).

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**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 microinvasion. The overall rate of metastases with lesions greater than 2.0 cm of invasion ranges from 5-19%.

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%
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 retromolar 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-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, pseudoangiomaticatous 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-
Keratinocytic tumours 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 polygonal 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).

**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.

**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 (1410), 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 (2567,2572). Human papillomavirus (HPV) genomes have been demonstrated in situ hybridization in the nuclei of keratinocytes in the stratum malpighii and stratum corneum of the BD lesions. HPV types 16 and 18 have been linked to lesions of genital BD and non-condylomatous genital warts, i.e., bowenoid papulosis (1098). HPV is less commonly associated with nongenital BD. HPV types 15 and 16 have been identified in some cases of BD on the distal extremities. Evidence of other papillomavirus types, including HPV31, 54, 58, 61, 62 and 73, have also been identified in some cases of BD. Aberrations in local and systemic immunity, trauma, chronic irritation, mutagenic factors, and tobacco exposure are other possible etiologies of BD.

**Localization**
Based upon a large series of 1001 biopsy-proven BD in Australia, most lesions occurred on a sun-exposed glabrous area (1315). About one-third (33%) of the lesions occurred in the head and neck areas, especially the face. Men had predominance of lesions on the scalp and ears, whereas women had a predominant involvement of the legs and cheeks. BD rarely affects the nail bed and periungual area (2070).

**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 polypoid or verrucoid, frequently pigmented. Erythroplasia of Queyrat (EPQ) presents as an asymptomatic,

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**Fig. 1.21**
A Bowen disease. Sharply circumscribed, bright red plaque of erythroplasia of Queyrat (EPQ).
B Bowen disease. Erythematous, scaly, fissuring plaques of BD on lower leg of a middle-aged woman.
bright red, velvety to shiny, sharply circumscribed plaque. The mucocutaneous junction of the glans penis, coronal 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 carcinoma. The invasive carcinomas are larger (up to 15 cm), rapidly growing tumours that occur in pre-existing scaly plaques.

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 carcinoma than does BD involving glabrous skin (875). Although evidence for the association of BD and internal malignancies 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 hyperchromatism, pale-staining to vacuolated cells, occasional multinucleated cells, individual cell keratinization (dyshkeratosis), and abnormal mitoses are noted. These changes are confined by an intact dermeoepidermal 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 koilocytotic viral cytopathic change and exhibit a pagetoid appearance. The acrotrichium 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 squamous, 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 maturation. 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 koiocytic 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 basilar 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 cytokeratins 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 localization of keratins and involucrin, the atypical cells of BD exhibit 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 suppressor 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 \(^1\). It was later defined \(^2\) as an entity involving the genitalia or perigenital areas. Isolated cases of extragenital Bowenoid papulosis have been described \(^3,4\).

**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 \(^5\). 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 \(^6\). 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 \(^7\). Electron microscopy has shown structures resembling viral particles \(^8\) 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 \(^9\) and spontaneous regression has occasionally occurred; however, close follow up is essential.
Actinic keratosis

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.

Macroscopy
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: hypertrrophic, atrophic, Bowenoid, acantholytic, pigmented and lichenoid (233,1446). Most lesions reveal parakeratosis and hypergranulosis. Disordered keratinocyte maturation with cytologic atypia is present, including nuclear enlargement, hyperchromasia, pleomorphism, nucleolar 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 cytosome 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 have 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).

Immune responses and adjacent normal keratinocytes modulate the behaviour of AK (791). Metastases from invasive carcinomas arising in AK are infrequent if the lip is excluded, occurring in 0.5-3% of such carcinomas (1459,1630).

**Arsenical 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-

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**Fig. 1.27** Arsenical keratosis. **A** Arsenical keratosis with vacuolation of the keratinocytes. **B** Arsenical keratosis showing acanthotic epidermis, some vacuolation of the keratinocytes and dysplasia.
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 seborrhoeic 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).
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 acuminata (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. Autoinoculation 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).

HPV structure and lifecycle
HPVs are 55 nm diameter, non-enveloped, double-stranded DNA viruses. The icosahedral capsid surrounds the viral genome which is approximately 8kb in length and is composed of the upstream regulatory region containing the origin of replication and control elements for transcription and replication, the early region containing the open reading frames for viral genes that are principally expressed early in the papillomavirus lifecycle (E1, E2, E4, E5, E6, E7), and the late region encoding the viral capsid proteins (L1, L2). Productive infection and induction of hyperproliferation are initiated when the virus enters proliferating basal epithelial cells, and this requires abrasion or other minor trauma to the epithelium. The HPV lifecycle is only completed in fully differentiated squamous epithelia since the programme of viral gene expression is intimately linked to the differentiation state of keratinocytes. HPV does not encode

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,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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>Prominent</td>
<td>Central, small, shrunken nuclei within proliferating rete ridges (granular)</td>
<td></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></td>
<td>60 (Ridged wart)</td>
<td>Acanthosis and mild papillomatosis; endophytic</td>
<td>Eosinophilic, homogeneous and solitary inclusions</td>
</tr>
<tr>
<td></td>
<td>65 (Pigmented plantar wart)</td>
<td>Prominent; endophytic</td>
<td>Eosinophilic, homogeneous and solitary inclusions</td>
</tr>
<tr>
<td>Verruca Plana</td>
<td>3</td>
<td>Prominent; endophytic</td>
<td>Intracytoplasmic, heavily stained keratohyaline material with filamentous inclusions that encase the vacuolated nucleus</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, palmar plantar 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 sub-clinical 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.

![Fig. 1.29 Verruca vulgaris showing the Koebner phenomenon. Note the linear arrangement of the lesions as a consequence of scratching.](image)

![Fig. 1.30 Verruca vulgaris. There is hyperkeratosis, papillomatosis and interning of the elongated rete ridges.](image)
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 papillomatosis, 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.
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 keriocytosis, vacuolated keratinocytes with perinuclear clearing around centrally located nuclei (so-called “birds-eye cells”) and hypergranulosis. 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).

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 may be 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 folliculosebaceous 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, keratotic, 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 “jami-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 conclude 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. While most seborrhoeic keratoses 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, dialated 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.

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 interconnected 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 (1743). 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 (742).

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 (1576,1959). It was thought to represent a particular type of actinic keratosis (1875,2095), Bowen disease (2038), or a distinct entity (69,1871,2039).

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 (2165). Hypopigmentation is also seen (69). Dermatoscopy may rule out melanoma.

Histopathology
Large cell acanthoma is a sharply delimited lesion standing out by its unique 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 (2039). The granular layer is thick, there is usually ortho/parakeratosis and the rete ridges may be slightly bulbous. The growth fraction is low (86,1576) although there is a considerable proportion of both aneuploid and hyperdiploid cells (86).

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 (190,1701).

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 tumors 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-colored, 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
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, seborrhoeic 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 seborrhoeic 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 seborrhoeic 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.