Melanocytic Tumours

Melanocytic skin tumours include a large variety of benign and malignant neoplasms with distinct clinical, morphological and genetic profiles. From a clinical and public health point of view, the malignant melanomas are the most important group of skin cancers. Although less common than the familiar basal and squamous cell tumours of the skin, they are much more frequently fatal, due to their intrinsic tendency to lymphatic and haematogenic metastasis. Intermittent high-dose UV radiation is the major environmental risk factor, often in combination with endogenous factors, including genetic susceptibility. Malignant melanoma affects predominantly fair-skinned Caucasians, although they also occur in ethnic groups characterized by a more pigmented skin. The sharp increase in incidence rates largely reflects lifestyle attitudes towards vacational sun exposure, but recent data indicate that this trend is now levelling off. Primary prevention and screening for early lesions are considered the most promising approach to a reduction of melanoma mortality.
### WHO histological classification of melanocytic tumours

<table>
<thead>
<tr>
<th>Malignant melanoma</th>
<th>Morphology Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading melanoma</td>
<td>8743/3</td>
<td>Naevus of Ito and Ota</td>
</tr>
<tr>
<td>Nodular melanoma</td>
<td>8721/3</td>
<td>Mongolian spot</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>8742/2</td>
<td>Blue naevus</td>
</tr>
<tr>
<td>Acral-lentiginous melanoma</td>
<td>8744/3</td>
<td>Cellular blue naevus</td>
</tr>
<tr>
<td>Desmoplastic melanoma</td>
<td>8745/3</td>
<td>Combined naevus</td>
</tr>
<tr>
<td>Melanoma arising from blue naevus</td>
<td>8746/3</td>
<td>Melanotic macules, simple lentigo and lentiginous naevus</td>
</tr>
<tr>
<td>Melanoma arising in a giant congenital naevus</td>
<td>8761/3</td>
<td>Dysplastic naevus</td>
</tr>
<tr>
<td>Melanoma of childhood</td>
<td>8762/2</td>
<td>Site-specific naevi</td>
</tr>
<tr>
<td>Naevoid melanoma</td>
<td>8720/3</td>
<td>Acral</td>
</tr>
<tr>
<td>Persistent melanoma</td>
<td>8720/3</td>
<td>Genital</td>
</tr>
<tr>
<td>Meyerson naevus</td>
<td>8720/3</td>
<td>Persistent (recurrent) melanocytic naevus</td>
</tr>
<tr>
<td>Spitz naevus</td>
<td>8720/3</td>
<td>Malignant melanocytic naevi</td>
</tr>
<tr>
<td>Pigmented spindle cell naevus (Reed)</td>
<td>8721/3</td>
<td>Dermal melanocytic lesions</td>
</tr>
<tr>
<td>Halo naevus</td>
<td>8721/3</td>
<td>Spitz naevus</td>
</tr>
</tbody>
</table>

### Benign melanocytic tumours

<table>
<thead>
<tr>
<th>Congenital melanocytic naevi</th>
<th>Morphology Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial type</td>
<td>8761/0</td>
<td>Mongolian spot</td>
</tr>
<tr>
<td>Proliferative nodules in congenital melanocytic naevi</td>
<td>8762/1</td>
<td>Blue naevus</td>
</tr>
</tbody>
</table>

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1. **M**orphology code of the International Classification of Diseases for Oncology (ICD-O-3) [786] and the Systematized Nomenclature of Medicine (http://snomed.org).

   Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for non-invasive tumours, and /1 for borderline or uncertain behaviour.
### TNM classification of malignant melanoma

**TNM classification**

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

**N - Regional lymph nodes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in one regional lymph node</td>
</tr>
<tr>
<td>N1a</td>
<td>only microscopic metastasis (clinically occult)</td>
</tr>
<tr>
<td>N1b</td>
<td>macroscopic metastasis (clinically apparent)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in two or three regional lymph nodes or intralymphatic regional metastasis</td>
</tr>
<tr>
<td>N2a</td>
<td>only microscopic nodal metastasis</td>
</tr>
<tr>
<td>N2b</td>
<td>macroscopic nodal metastasis</td>
</tr>
<tr>
<td>N2c</td>
<td>satellite or in-transit metastasis without regional nodal metastasis</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in four or more regional lymph nodes, or matted metastatic regional lymph nodes, or satellite or in-transit metastasis with metastasis in regional lymph node(s)</td>
</tr>
</tbody>
</table>

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

**M - Distant metastasis**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Skin, subcutaneous tissue or lymph node(s) beyond the regional lymph nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung</td>
</tr>
<tr>
<td>M1c</td>
<td>Other sites, or any site with elevated serum lactic dehydrogenase (LDH)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>pT0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>pTis</td>
<td>Melanoma in situ (Clark level I) (atypical melanocytic hyperplasia, severe melanocytic dysplasia, not an invasive malignant lesion)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1</td>
<td>Tumour 1 mm or less in thickness</td>
</tr>
<tr>
<td>pT1a</td>
<td>Clark level II or III, without ulceration</td>
</tr>
<tr>
<td>pT1b</td>
<td>Clark level IV or V, or with ulceration</td>
</tr>
<tr>
<td>pT2</td>
<td>Tumour more than 1 mm but not more than 2 mm in thickness</td>
</tr>
<tr>
<td>pT2a</td>
<td>without ulceration</td>
</tr>
<tr>
<td>pT2b</td>
<td>with ulceration</td>
</tr>
<tr>
<td>pT3</td>
<td>Tumour more than 2 mm but not more than 4 mm in thickness</td>
</tr>
<tr>
<td>pT3a</td>
<td>without ulceration</td>
</tr>
<tr>
<td>pT3b</td>
<td>with ulceration</td>
</tr>
<tr>
<td>pT4</td>
<td>Tumour more than 4 mm in thickness</td>
</tr>
<tr>
<td>pT4a</td>
<td>without ulceration</td>
</tr>
<tr>
<td>pT4b</td>
<td>with ulceration</td>
</tr>
</tbody>
</table>

Note: *pTX includes shave biopsies and regressed melanomas.

### Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>pTis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>pT1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>pT1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>pT1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>pT2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>pT2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>pT3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>pT4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>pT4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any pT</td>
<td>N1, N2, N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>pT1a-4a</td>
<td>N1a, 2a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>pT1b-4a</td>
<td>N1b, 2b, 2c</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>pT1b-4b</td>
<td>N1b, 2b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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3 Clinical staging includes complete excision of the primary melanoma (pT) with clinical/radiological assessment for regional and distant metastases.

Pathologic staging includes complete excision of the primary melanoma (pT) and pathologic assessment of the regional lymph nodes (pN) after partial or complete lymphadenectomy. Stage 0 or stage IA patients do not require pathological evaluation of their lymph nodes.
Malignant melanoma: Introduction

Incidence and mortality

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

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

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

Geographical differences

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

Melanoma in Caucasians

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

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

Migrant studies

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

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

Melanoma in non-Caucasians

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

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

**Time trends**

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

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

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

**Stabilisation of melanoma incidence rates**

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

A recent plateau in melanoma mortality rates (in some cases followed by incidence rates) is reported in high-incidence countries, such as Australia, USA, Sweden, Norway and Germany (609, 1353,1761,2120,2245). Only the mortali-
There has been much discussion and debate as to the reasons underlying the dramatic increases in melanoma incidence and mortality, and in particular, whether they are real or due to artefacts, via, for example, increased efforts at screening and diagnosing the disease, changes in diagnostic criteria, or the existence of a non-metastasizing biologically benign form of melanoma. Although some artefacts may have contributed to the increases, a substantial part of the increases is assumed to be genuine (610). Both familial and environmental factors play a role in the etiology of melanoma. The familial/genetic components include skin type, number of naevi, having clinical atypical naevi, and having a family history of skin cancer. They are the most important predictors of melanoma risk. As it is not likely that there has been a substantial change over time in familial/genetic risk factors in most populations, these cannot have contributed substantially to the observed increases in melanoma incidence over the past 50 years.

**Etiology**

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**Exposure to UV radiation**

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

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

**Occupational vs. recreational exposure**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ABCD rule

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

Pigmentation and growth

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

Regression

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

**Clinical variants**

**Amelanotic melanoma**

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

**Mucosal melanoma**

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

**Subungual melanomas**

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

**Ulceration**

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

**Verrucous phenotype**

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

**Dermatoscopy**

Besides clinical examination, dermatoscopy (dermoscopy, skin surface microscopy, epiluminescence microscopy) has been increasingly regarded as a valuable aid in diagnosis of early melanoma clinically. Dermatoscopic instruments enlarge the lesion 6-100-fold, thus allowing detection of structures and signs not visible to the naked eye. In addition, connection of the dermatoscopic devices to a computer allows one to take standardized digital pictures that can be compared over time, thus being much more sensitive for detection of minimal structural changes of the examined lesion (719). Finally, computer-assisted diagnostic systems based on dermatoscopic images are available as aids for the evaluation of suspicious pigmented lesions (91). Several dermatoscopic diagnostic approaches have been proposed, all of them relying on the examination of distinct patterns and structures. Of particular value in the diagnosis of melanoma are the presence of an irregular pigment...
network (uneven thickness of the lines, presence of broad lines at the periphery of the lesion), of black or brown dots irregularly distributed within the lesion, of irregular lines at the periphery of the lesion that are not clearly combined with the pigment network (streaks), of a blue-whitish veil corresponding to infiltrates of melanophages below a thick epidermis with hypergranulosis, of an atypical vascular pattern, and of regression structures. A 7-point checklist for dermatoscopic scoring of atypical melanocytic lesions using the aforementioned criteria has been proposed, and it has been suggested that this approach allows diagnosis of melanoma with a sensitivity of 95% and a specificity of 75% (91,1671). Other proposed approaches include the Menzies method and the ABCD rule (91). Besides dermatoscopy, the use of several other devices has been proposed for the early in vivo diagnosis of melanoma, including confocal laser microscopy (1509).

**Histopathology**

**Architectural criteria in the epidermis**

**Lesional breadth**

A proliferation of melanocytes wholly within the epidermis can range in size from >1 mm to a patch many cm in width. Both melanocytic naevi (conventional and Spitz) and melanoma begin as proliferations in which single melanocytes predominate. By the time most melanomas can be recognized as such clinically they are over 4 mm in diameter, and often far broader (730). While a large lesional diameter is a finding favouring melanoma, there are many exceptions.

**Symmetry of changes in the epidermis**

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

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

**Circumscription**

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

**Predominance of single cells vs. nests**

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

The distribution of single melanocytes is also noteworthy. One can imagine a dotted line connecting the tops of dermal papillae with one another. Very few melanocytes should reside in the epidermis above that line. Confluence of melanocytes is another...
clue to the diagnosis of melanoma. Confluent single melanocytes replace the basal layer in a manner such that, at least focally, keratinocytes do not seem to intervene between them. Confluence of nests of melanocytes is a more subjective determination.

**Scatter of melanocytes above the junction**

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

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

**Configuration of the epidermis**

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

**Kamino bodies**

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

**Cytological features of melanoma in the epidermis**

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

Small melanocytes with scant cytoplasm and angulated, darkly stained nuclei are particularly apt to be found in melanomas in severely sun-damaged skin (lentigo maligna and lentigo maligna melanoma). A similar appearance can be induced by processing artefact, and by the use of some alcohol-based fixatives instead of formalin. Large round or oval, or epithelioid melanocytes occur in both benign proliferations and in melanoma. Such cells often have abundant pale cytoplasm, with “dusty” (fine and evenly dispersed) melanin. These cells are typically seen in the intraepidermal components of melanomas of all types. Large, pale melanocytes are also present in naevi of the scalp (especially in children and teens), breast and genitalia, and in some dysplastic naevi (1532). Spindled melanocytes occur within the epidermis in the junctional nests of dysplastic naevi and in Spitz naevi, as well as in melanoma, where their orientation is haphazard (some nests may be vertical and some horizontal). The nuclei of spindled melanoma cells are more often pleomorphic, and there is heterochromasia, i.e. some may be vesicular and some stain darkly. Dendritic melanocytes are present in melanomas in dark skin patients in diverse settings, and light skinned ones in so-called lentigo maligna and the lentigo maligna pattern of melanoma, and in melanomas of acral-volar skin, the nail bed and of mucous membranes. The nuclei of dendritic melanocytes may be inconspicuous. The findings of dendrites that ascend to the mid-spinous zone, and...
especially variability in the widths of dendrites at the same level of the epidermis (anisodendrocytosis) are useful clues to melanoma in these settings. The extreme cytologic atypia typically seen in thick melanomas in the dermis and in metastases of melanoma, with very large, irregularly shaped and brightly eosinophilic nucleoli is not usually to be found in the intraepidermal component of a melanoma.

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

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

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

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

In addition to nuclear maturation, the amount of cytoplasm is less at the base of a benign melanocytic neoplasm than in its upper nests. If the cytoplasm of the upper cells of a naevus is pigmented, its lower cells tend to be less pigmented or achromic. The sizes of aggregations of melanocytes also should be smaller toward the bottom of a benign neoplasm of melanocytes.

The scientific basis of maturation rests on changes in metabolism (less tyrosinase activity and more acetylcholinesterase activity) and telomeric exhaustion (865,1620).

Maturation occurs to a limited extent in some melanomas, but in most there are cells at the base of the lesion nearly as large as those at the top, and dispersion from large nests to small ones and single cells is often absent (1989). Pigmentation near the base of a melanocytic neoplasm can also be a clue to melanoma, but it commonly occurs in blue naevus.

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

**Cytologic features of melanoma in the dermis**

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

**Radial and vertical growth**

**Radial growth phase**

Most melanomas evolve through an initial stage of tumor progression, as a flat or plaque-like lesion which expands along the radii of an imperfect circle. Because of this clinical analogy, this phase has been termed the “radial growth phase” (494).

The radial growth phase may be in situ (confined to the epidermis), or in situ and invasive, but in the latter case the cells do not have capacity for proliferation in the dermis (674,832). Proliferation in the epidermis may give rise to a pattern of single cells, or of clusters or nests of atypical neoplastic melanocytes. Like the cells of junctional nevi, which may migrate into the dermis to form compound nevi, the cells of in situ melanomas may migrate into the papillary dermis. In the dermis, these cells may either undergo apoptosis and disappear (1070), or may survive without proliferating. In the latter case, the lesional cells may persist in the dermis, but they do not expand to form a tumorigenic nodule.

**Vertical growth phase (tumorigenic)**

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

### Metastatic spread

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

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

<table>
<thead>
<tr>
<th>Table 2.02</th>
<th>Melanoma antigens</th>
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</thead>
<tbody>
<tr>
<td><strong>Type of antigen</strong></td>
<td><strong>Antigen</strong></td>
</tr>
<tr>
<td>Differentiation antigens</td>
<td>Tyrosinase, gp100, Melan-A/MART-1, TRP-1, TRP-2, MC1R, AIM-1</td>
</tr>
<tr>
<td>Gangliosides</td>
<td>GM 3, GD 3, GD 2, GM 2, 0-acetyl GD 3</td>
</tr>
<tr>
<td>Mutated proteins</td>
<td>CDK4, B-catenin, CDC27, MUM-2, triosephosphate isomerase</td>
</tr>
<tr>
<td>Products of unusual DNA transcripts</td>
<td>TRP-2, N-acetylglucosaminyl transferase</td>
</tr>
<tr>
<td>Cancer / testis antigens (CTAs)</td>
<td>MAGE, BAGE, GAGE, RAGE, NY-ESO-1</td>
</tr>
</tbody>
</table>
passage to other nodes in the regional node field. Thus the SN is most likely to contain tumour cells, and if none are present in this node, tumour cells are unlikely to be present in other nodes in the node field. Within 3 years of the landmark publication by Morton et al (1915), confirmation of the accuracy of such assessment was provided by studies in the USA (1915) and Australia (2347). It soon became clear that identification of this node was most accurate if three methods were used: a preoperative lymphoscintigram, injection of blue dye around the primary melanoma site immediately preoperatively, and the use of a hand-held gamma probe intraoperatively. Preoperative lymphoscintigraphy for many melanoma patients before SN biopsy provided important new insights into cutaneous lymphatic drainage pathways (2348,2396) and this new information highlighted the importance of preoperative lymphoscintigraphy before undertaking a SN biopsy procedure. The prognostic value of determining SN status has now been shown in several large studies. All show a large difference in probability of 5-year survival between patients who are SN positive and those who are SN negative, independently of other prognostic variables. Results from the Sydney Melanoma Unit (2565) are typical, with a 5-year survival rate of 56% for SN positive patients (n=145) and 90% for SN negative patients (n=846). Prognostic information from SN biopsies may be further refined by PCR to detect melanoma-specific mRNA in lymph nodes that are negative by standard histopathological techniques (1916). SN assessment not only provides important prognostic information; recent clinical trials suggest that as an removal, with complete regional node field dissection if micrometastatic melanoma is found, improves the survival of patients (1655A).

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

Most melanomas are localized in high incidence countries and the proportion that are localized continues to increase with time. Of the cases reported in the U.S. SEER program 1992-1998, 82% had localized disease, 9% regional disease, 4% distant metastases, and 6% were unstaged (186). Young patients and women are often diagnosed with melanomas that have a thinner Breslow thickness than older patients and men. Because of the shift in the stage distribution of melanomas towards thinner lesions, together with a disproportionate increase in incidence relative to mortality, some have questioned whether some of these thin lesions that were removed would have ever progressed to metastatic disease (353).
Melanocytic lineage are identified, but of melanin synthesis. Hereby cells of the differentia tion which is manifested by signs These markers indicate melanocytic dif ferentiation markers.

Three groups of markers can be distinguished: Melanoma markers

The term “melanoma antigen” is used two-fold. Firstly, it refers to a large variety of molecules recognized by (monoclonal) antibodies, that were generated to explore their potential as biological and/or clinical markers. Second ly, melanoma antigen in a strict sense implies a tumour molecule that evokes an immune response in the autologous host (1944). Some overlap exists between genuine melanoma antigens and melanoma markers. Melanoma antigens currently are used in vaccination trials.

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Melanoma markers

Three groups of markers can be distinguished:

Differentiation markers

These markers indicate melanocytic differentiation which is manifested by signs of melanin synthesis. Hereby cells of the melanocytic lineage are identified, but also ectopic melanin synthesis in cells of other lineages. Differentiation markers show a broad expression in many benign melanocytic lesions and (most) primary melanomas. However, in melanoma metastases expression decreases which is accompanied by heterogeneity.

Progression markers

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

Other markers

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

Clinical applications

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

Differential diagnosis of poorly differentiated malignant tumours

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

Immunotherapy

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

Genetic susceptibility

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

Table 2.04

Prognostic indicators for melanoma.

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Most favourable when:</th>
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<tbody>
<tr>
<td>Breslow thickness</td>
<td>Thin (&lt;1.51 mm)</td>
</tr>
<tr>
<td>Histology</td>
<td>Superficial spreading melanoma</td>
</tr>
<tr>
<td>Age</td>
<td>Young</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Body site</td>
<td>Not on the trunk, hands, feet</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Absent</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>Low</td>
</tr>
</tbody>
</table>
Other genes, such as MC1R (Melanocortin 1 Receptor) and DNA repair genes, are likely to be more important in determining susceptibility for melanoma in the general population. The MC1R gene is involved in skin and hair pigmentation and in senescence and immunity (176,251,2385). Patients with inherited abnormalities in the DNA repair system, like xeroderma pigmentosum patients, are at a 1000-fold increased risk (891).

**Prognosis and predictive factors**

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

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

**Morphological prognostic factors**

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

**Clark’s levels of invasion**

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

**Breslow’s thickness**

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

**Ulceration**

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

**Mitotic rate**

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

**Tumour infiltrating lymphocytes**

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

**Lymphovascular invasion**

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

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

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

Patient gender and lesional cell location
In most series, even when other prognostic factors are controlled, female patients have better survivals, and the survival is better for patients whose lesions are on the limbs compared to the trunk or extremities \{491\}.

Immunoprofiling for the assessment of prognosis
Two strategies are followed:
1. Identification of markers suggestive of aggressive subpopulations in primary melanoma \{1990\}. For this purpose late progression markers are used. Only a limited number of progression markers have prognostic implication independent of the conventional dominant factors, i.e. tumour thickness and ulceration. A list of prognostic markers is presented in Table 2.5. It should be noted here that the clinical relevance of these markers is increasing as the primary melanomas currently diagnosed are relatively thin (1.0-1.5 mm) and rarely show ulceration. It is expected that a set of prognostic markers may help to select melanoma patients for adjuvant therapy. Such a set may be designed on the basis of the outcome of ongoing expression array studies.
2. Microstaging. The presence of melanoma deposits in various stages of the disease is assessed by the demonstration of differentiation markers. However, they may decrease during tumour progression and do not reveal the aggressiveness of the tumour cells. Nevertheless, the extension of the primary tumour that includes thickness measurement and identification of microsatellites, can be facilitated by S-100 or MART-1 immunohistochemistry. This also is applicable for the detection of melanoma cells in sentinel nodes. Immunohistochemistry on serial sections is preferred to molecular staging of sentinel nodes as it has a similar sensitivity, a higher specificity and it preserves morphology.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Expression</th>
<th>Prognosis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>PCNA</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>Cyclin A</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>p36</td>
<td>↓</td>
<td>–</td>
</tr>
<tr>
<td>αvβ3</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>CD44</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>MMP-2</td>
<td>↑</td>
<td>+</td>
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<tr>
<td>t-PA</td>
<td>↑</td>
<td>+</td>
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<tr>
<td>gp100</td>
<td>↓</td>
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<tr>
<td>Mitf</td>
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<td>+</td>
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<tr>
<td>c-kit</td>
<td>↓</td>
<td>–</td>
</tr>
<tr>
<td>c-myc</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>p53</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>Osteonectin</td>
<td>↑</td>
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</tr>
</tbody>
</table>

¹: Unfavourable: +: favourable
Superficial spreading melanoma

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

ICD-O 8743/3

Synonym
Pagetoid melanoma.

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

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

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

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

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

With development of invasive melanoma, an asymmetric outline becomes a major characteristic. Extensive and highly irregular junctional tumour nests are found at a variable distance to each other.
other and may merge. There is often a lack of maturation, manifested by a failure of nests, cells, nuclei or nucleoli to become smaller towards the base of the lesion. Pigment is often irregularly distributed. Mitoses, sometimes atypical, are often seen whereas necrotic melanocytes are rarely identified. A lymphocytic infiltrate may be present at the base of the neoplasm or may infiltrate among its cells (so called tumour infiltrating lymphocytes or TILs). Melanoma may undergo regression, which clinically and grossly most often involves a portion of the lesion, or occasionally its entirety. Histologically this regression may be complete or partial within a given area. Complete regression of a portion of a melanoma (“segmental regression”) is manifested by absence of melanocytes in the affected area. In partial regression, there is a strikingly diminished number of melanocytes compared to the remainder of the lesion. In both forms there is fibrosis of the papillary dermis, vascular proliferation and ectasia, and variably dense infiltrates of lymphocytes and melanophages. The epidermis may show loss of rete ridges. The type of regression described above affects the radial growth phase. Occasionally, a vertical growth phase may undergo regression, and sometimes the regressed portion may be replaced by a large mass of melanophages, representing a phenomenon called “tumoural melanosis”.

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

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

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

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

ICD-O code 8721/3

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

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

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

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

Macroscopy
As in the clinical features

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

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

Fig. 2.15 Nodular melanoma. A On scanning magnification the tumour has a polypoid configuration with slight asymmetry. Cohesive nodules of tumour cells fill the dermis. B Superficial portion of the tumour. Epithelioid melanoma cells are present as single units and in nests that vary in size and shape along the dermoeipidermal junction and above it. Similar nests are present in the upper dermis along with numerous melanophages and lymphocytic infiltrates. Some of the epithelioid melanoma cells contain fine melanin granules.
High nuclear-to-cytoplasmic ratios are often noted. The tumour cells fail to “mature” with progressive descent into the dermis. The cytoplasm of the epithelioid cells often has eosinophilic granular qualities. It may contain melanin granules that vary in size, or appear fine and “dusty”. There is absence of melanin in the amelanotic tumours. The surrounding stroma may demonstrate variable mononuclear cell infiltrates, fibroplasia, telangiectasia, and melanophages.

**Immunoprofile**

S-100 protein, HMB-45, Melan A (MART-1), MAGE-1, NKI/C-3, tyrosinase, melanoma cell adhesion molecule (MelCAM) MUC18 and microphthalmia transcription factor (MITF), are expressed by most melanomas (732,1500,1855). Melanoma cells also express bcl-2 protein, neuron specific enolase and vimentin (626,1861,2131). Antigens which may demonstrate higher rates of expression in melanoma cells than in naevus cells include Ki-67 (MIB-1), proliferating nuclear antigen (PCNA), p53, cyclin D1, and p21 WAF1(9). The loss of expression of CDKN2A (cyclin dependent kinase inhibitor), and the increased expression of β3 integrin, have been associated with vertical growth phase and more invasive forms of melanomas (1029,1500,1904,2277,2278,2406).

**Electron microscopy**

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

**Precursor lesions and histogenesis**

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

**Somatic genetics**

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

**Genetic susceptibility**

The proportion of melanomas that have a familial basis ranges from 6% to 14%. Approximately 20% of all individuals with a family history of melanoma have mutations in CDKN2A which maps to chromosome 9p21. In a very few families CDK4 mapping to chromosome 12q14 has been found to be mutated (1851).

**Prognosis and predictive factors**

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

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

ICD-O code 8742/2

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

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

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

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

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

**Histopathology**

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

A lymphocytic infiltrate and focal fibroplasia are frequently present in the papillary dermis underlying LM, with severe solar elastosis and telangiectasia. Regression, shown by fibrosis, hypervascularity, melanophages and a patchy lymphocytic infiltrate, is a common feature and should prompt a careful search for invasion by atypical melanocytes. The presence of regression at a lateral margin of excision should be emphasized in the report as an indication for re-excision, even when the margins appear clear of atypical melanocytes. In LMM, dermal invasion occurs in association with LM. The invasive component may consist of atypical melanocytic spindle cells more frequently than is seen in the other common forms of cutaneous melanoma, but epithelioid, small naevoid and tumour giant cells may also be present in varied proportions. The cells of these various types may occur in cohesive groups, strands or as single cells in a diffuse pattern, often associated with lymphocytes and melanophages. The degree of pigmentation varies, including cells with abundant clear cytoplasm adjacent to cells in which the morphologic detail may be obscured by coarse melanin granules. The invasive component in LMM may be desmoplastic and/or neurotropic with very subtle, diffuse invasion that predisposes to incomplete excision and true local recurrence. Dermal invasion may also originate from atypical melanocytes in the walls of hair follicles and sweat ducts, thus creating a problem in measurement of tumour thickness because it is inappropriate to measure tumour thickness from the granular layer of the epidermis in this instance.

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

**Differential diagnosis**

In cases of extensive amelanosis (amelanotic LM) \(60\), the distinction between in-situ squamous cell carcinoma or extramammary Paget disease may be difficult in routine sections, necessitating the use of special stains to demonstrate epithe-
lial mucin in extra-mammary Paget disease, and immunostaining, including the use of antibodies to cytokeratins, melan-A and S-100 protein and, as further aids to the diagnosis of Paget disease, carcinoembryonic antigen, and BerEP4.

The distinction between LM and benign forms of junctional melanocytic proliferation is made on the basis of the characteristic cytologic atypia, confluent growth of atypical cells along the junction with frequent extension down the walls of adnexal structures and, commonly, extension of growth above the basal layer in pagetoid pattern.

**Histogenesis**

LM develops from epidermal melanocytes, most likely due to the cumulative DNA damage resulting from long-term sun exposure (1048). A recent study of the differential expression of proliferation- and apoptosis-related markers in lentigo maligna and the keratinocytes in solar keratosis has found that the epidermis in LM shows overall low proliferation and a low apoptotic tendency, perhaps aiding aberrant melanocyte proliferation in the early stages of melanoma development (718).

**Somatic genetics**

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

**Prognosis and predictive factors**

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

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Fig. 2.19 Lentigo maligna. Focal pagetoid growth is present in addition to junctional proliferation including small nests of atypical melanocytes.
Definition
Acral lentiginous melanoma (ALM) is a distinct variant of cutaneous melanoma, which occurs on the palms, soles, and subungual sites, and has a characteristic histologic picture. Following the three other major clinicopathological subtypes of melanoma, i.e. superficial spreading melanoma, lentigo maligna melanoma, and nodular melanoma, ALM was proposed as the fourth subtype by Reed in 1976 (1905). In this article, we also use the term acral melanoma and define it as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails. The reason for this usage is described below.

ICD-O code 8744/3

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

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

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

Localization

The term acral has been used differently throughout the literature. Most publications use acral for the non-hair bearing, i.e. glabrous skin of the palms and soles, and the nail bed, whereas others also include the dorsal aspect of the hands and feet under this term. In a German study, using the latter definition, acral melanoma occurred on the feet in 87% cases (plantar sites, 57%; subungual, 5%; and dorsum, 9%) and on the hands in 23% (palm, 1%; subungal, 14%; and dorsum, 9%) (1337). Thus, the plantar sites were greatly more often affected than the palmar sites (1337,2130,2201, 2220,2296). In contrast to ALM, superficial spreading melanoma occurs more commonly on the sun-exposed dorsal aspects of the hands and feet, whereas nodular melanoma occurs on all acral sites with relatively equal frequency (1337). In addition to the sole, nail plate is an especially frequent site with a frequency of 16-19% (1337,2130). In contrast to ALM, superficial spreading melanoma occurs more commonly on the sun-exposed dorsal aspects of the hands and feet, whereas nodular melanoma occurs on all acral sites with relatively equal frequency (1337). In addition to the sole, nail plate is an especially frequent site with a frequency of 16-19% in ALM (1337,2130). The radial growth phase of ALM is characterized by a macular pigmented lesion with highly irregular, notched borders and varying shades of pigmentation. Within a background pigmented macule, acral melanomas often develop a clinically apparent vertical growth phase. This is manifest as an elevated papule or nodule, sometimes with a verrucous surface, and corresponds to the histological vertical growth phase of malignant melanocytes. Ulceration is more often seen in ALM than in other types of melanoma. Subungual melanomas often begin as brown to black discolouration of the nail that frequently become bands or streaks of pigmentation. Thickening, splitting, or destruction of the nail plate may occur. The irregular macular hyperpigmentation, coloured tan to dark brown, is also recognized around the nail plate (2130). In one study, 17% of the patients noticed

Clinical features

Acran melanomas in the early stages appear as a pigmented macule similar to lentigo maligna. Acral melanomas commonly exhibit clinical evidence of a biphasic growth pattern, with a more rapid evolution from an entirely flat clinical lesion to a lesion containing an elevated focus than is observed in the other types of melanoma. The radial growth phase of ALM is characterized by a macular pigmented lesion with highly irregular, notched borders and varying shades of pigmentation. Within a background pigmented macule, acral melanomas often develop a clinically apparent vertical growth phase. This is manifest as an elevated papule or nodule, sometimes with a verrucous surface, and corresponds to the histological vertical growth phase of malignant melanocytes. Ulceration is more often seen in ALM than in other types of melanoma. Subungual melanomas often begin as brown to black discolouration of the nail that frequently become bands or streaks of pigmentation. Thickening, splitting, or destruction of the nail plate may occur. The irregular macular hyperpigmentation, coloured tan to dark brown, is also recognized around the nail plate (2130). In one study, 17% of the patients noticed
the pre-existence of some pigmented skin lesions, and 21% related a history of trauma (2130). Pigmented streaks are not uncommon in patients with deeply pigmented skin, nevertheless, a history of a new or recently changing pigmented lesion should prompt the consideration of a biopsy for histological evaluation of the lesion. In this case, reflection of the proximal nail fold to enable biopsy of the nail bed may be necessary for definitive diagnosis.

Unfortunately, clinical misdiagnosis is not uncommon in patients with ALM (409, 767,1327,1592,2222). Therefore, awareness of atypical presentations of ALM that may contribute to misdiagnosis or diagnostic delay assumes particular importance. ALM lesions are frequently treated or followed for considerable time under the clinical diagnosis of wart, callos, fungal disorder, subungal haematoma, keratoacanthoma, nonhealing ulcer, foreign body, naeuvus, ingrown toenail, etc (2222).

**Histopathology**

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

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

**Immunoprofile**

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

**Somatic genetics**

Comparative genomic hybridization (CGH) of melanomas on acral non-hair bearing skin showed distinct differences to melanomas on non-acral skin (171). A study of 15 acral melanomas and 15 superficial spreading melanomas from non-acral sites showed that all (100%) acral cases had gene amplifications, whereas amplifications were found in two of the superficial spreading melanomas (13%). The most common amplified region is chromosome 11q13 which occurred in 50% of these types of melanoma. A recent study has shown that cyclin D1 is one of several candidate genes in this region. This conclusion was based on the observation that amplification of the cyclin D1 gene was always accompanied with overexpression of the cyclin D1 protein, and that inhibition of cyclin D1 expression in vitro and in xenograft models led to apoptosis or tumour shrinkage (2072).

FISH studies on primary lesions of acral melanoma showed that the amplifications arise early in acral melanoma and can already be detected at the in situ stage (171). The in situ portion of acral melanoma may extend beyond what is recognizable histopathologically. FISH detected gene amplifications were identified in single basal melanocytes immediately adjacent to the in situ component of acral melanoma; they were equidistantly spaced and looked histopathologically inconspicuous (171). Based on the observation that these “field cells” were found at the histopathologically uninvolved excision margins of an acral melanoma that recurred multiple times the authors propose that field cells may be a form of minimal residual melanoma that leads to persistence if not removed. More recent studies using array CGH have confirmed the frequent gene amplifications in acral melanoma preferentially involving chromosome 11q13. In addition, the studies revealed that all melanomas showed these features, independent of their histological growth pattern, as long as they were located on glabrous, i.e. non-hair bearing skin of the palms and soles or subungal sites (Bastian et al, to be published). In addition, melanomas involving these anatomical sites also had a significantly lower mutation rate of the BRAF oncogene (6/39, 15%) than melanomas on the trunk (23/43, 53%) (1493). The molecular genetic analyses therefore suggest melanomas of the palms of soles and subungal sites represent a genetically distinct form of melanoma, independent of their histological growth pattern.

**Prognosis and predictive factors**

In general, the prognosis of invasive acral melanoma is poor. This can partly be explained by the above described diagnostic delay and increased tumour thickness at the time of diagnosis. However, there are some studies suggesting that acral melanomas may undergo a more aggressive course independent of tumours thickness (151,308, 661,1337). In a study from Germany, 63 out of 64 patients (98.5%) with melanoma of the sole subsequently developed metastases (775); a corresponding figure from Japan in 1983 was 35% (2130). The same hospital recorded that the 5-year survival rate of subungal melanoma increased from 53% in 1969-82 to 83% in 1983-93 (1221), presumably because of early awareness of lesions and development of treatment (2012). However, others have reported that ALM is not a significant prognostic indicator (661,2201), and adjustment for histologic and clinical stage renders the prognostic importance of anatomic location insignificant (151, 308). These conflicting results can in part be explained by the different definitions used for acral melanomas in the studies. Future studies using refined criteria including genetic information are necessary to assess the prognosis of this melanoma type.
**Definition**
Desmoplastic melanoma (DM) is a spindle cell melanoma in which the malignant cells are separated by collagen fibres or fibrous stroma. It displays variable cytological atypia, cellularity and stromal fibrosis and more often than not has an accompanying junctional component. Neurotropism is a common associated feature (in at least 30% of cases) and when it occurs such tumours are termed desmoplastic neurotropic melanomas (DNM). The neurotropism may be perineural or intraneural and often extends beyond the desmoplastic component. DM may also present as a recurrence or occasionally as a metastasis from other types of melanoma.

**ICD-O code** 8745/3

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

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

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**Fig. 2.22** Desmoplastic neurotropic melanoma. **A** Male, 73 yrs, cheek. A few atypical enlarged melanocytes are present in the junctional zone. The fibrohistiocytic pattern is accompanied by scattered lymphocytes, some in clusters. Mitoses are hard to find. **B** Female, 24 yrs, lip. There are "neural transforming" areas with thick neuroid bundles in the upper dermis. Note occasional atypical junctional melanocytes, a few subepidermal spindle cells and scattered lymphocytes. **C** Male, 73 yrs, cheek. Malignant spindle cells with elongated nuclei appear to be within and between collagen bundles. **D** Female, 24 yrs, lip. "Neural transforming" areas with neuroid bundle (top of picture) containing atypical elongated spindle nuclei. Intraneural and perineural involvement of a small nerve is also present. There is a prominent infiltrate of lymphocytes.
Desmoplastic melanoma and desmoplastic neurotropic melanoma

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

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

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

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

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

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

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

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

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

Negative. Microphthalmia transcription factor (MTF) is not a sensitive or specific marker (356,885,1294). Type IV collagen and laminin are frequently expressed in DM (1857). Vimentin is usually positive although positive staining does not usually assist in diagnosis.

Differential diagnosis

The differential diagnosis includes desmoplastic naevus (958), which like DM may have perineural extension but lacks asymmetry, mitotic activity, marked nuclear atypia and lymphoid infiltrates. Well established desmoplastic Spitz naevi may have many HMB45 negative spindle cells but these naevi are usually symmetrical with epidermal thickening, include at least a few plump cells and have rare or absent mitoses. Sclerosing cellular blue naevi, which are most frequent on the scalp, also lack mitoses and are more or less diffusely HMB45 positive. Immature scars, especially in re-excision specimens, may focally resemble DM as they may have some S-100 positive spindle cells (476,1951), foci of lymphocytes and mitoses.

Other differential diagnoses include dermatofibroma/fibrous histiocytoma, fibrosarcoma, “malignant fibrous histiocytoma”, malignant peripheral nerve sheath tumour and leiomyosarcoma. These tumours can usually be separated by morphology and appropriate immunohistochemistry.

Histogenesis

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

Somatic genetics

Chromosomal aberrations and gene mutations have been found in sporadic and familial melanoma (799). Allelic loss at the neurofibromatosis type 1 (NF1) gene locus is frequent in DM (931). Basic fibroblast growth factor (bFGF) and other fibrocytokines are often present in the nuclei of DMs (1335). Loss of heterozygosity of matrix interacting protein 1 (MIX1) is frequent (1893). No BRAF mutations were found in 12 desmoplastic melanomas (596), consistent with the finding that melanomas on chronically sun-exposed skin only rarely have BRAF mutations (358B,596,1493).

Prognosis and predictive factors

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

Immunoprofile

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

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Melanoma arising from blue naevus

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

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

ICD-O 8780/3

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

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

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

Etiology
The etiology of melanoma associated with blue naevus is unknown, but the presence of longstanding dermal melanocytosis is likely a risk factor. Ocular and oculodermal melanocytosis (naevus of Ota) is strongly associated with uveal melanoma (2192,2193) and has been reported with meningeal melanocytoma (blue naevus) of the brain (1877) and primary melanomas of the central nervous system (253,569,1104, 1713,1930,2046). Based on this association and numerous reports of melanoma of the face, orbit or brain associated with oculodermal melanocytosis patients presenting with naevus of Ota should be considered at lifetime risk for melanoma of the skin, orbit or central nervous system, a risk that maybe similar in nature to that identified for large congenital melanocytic naevi with melanoma and neurocutaneous melanocytosis (254).

Fig. 2.26 Melanoma arising from blue naevus. Note the presence of satellitosis (Courtesy of Dr. H. Kerl).

Fig. 2.27 Melanoma arising from blue naevus. A Scanning magnification showing a blue naevus with a nodule of malignant melanoma in deeper areas. B In deeper areas the nodule of malignant melanoma was composed of sheets of cells destroying pre-existing structures of the dermis.
Additional associations of unknown influence include subacute cutaneous lupus erythematosus, leukoderma, Becker’s naevus and prostate adenocarcinoma in one patient (1629), papillary thyroid carcinoma (94), acute lymphocytic leukaemia (2119), psoriasis (238), and oral contraceptives (1404). Phototherapy has been associated with cellular blue naevus development (810).

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

At scanning magnification, two histopathologic patterns are evident. One is represented by the benign component of the blue naevus, which may range from very focal to comprising the main bulk of the neoplasm. Often this benign component is represented by a cellular blue naevus and less frequently the lesion contains a common blue naevus. Most cases, however, show a combination of the so-called cellular and common blue naevi, making this distinction useless. The areas of cellular blue naevus consist of solid aggregations of closely arranged monomorphous ovoid cells with abundant pale cytoplasm containing little or no melanin and round vesicular nuclei with inconspicuous nucleoli. In contrast, the areas of common blue naevus are made up of elongated spindled bipolar melanocytes, with long branching dendritic processes most of them filled with abundant granules of melanin. Melanophages and sclerotic bundles of collagen are also frequently observed between the fascicles of dendritic melanocytes.

Although the malignant component may involve the superficial dermis and ulcerate the epidermis, more often it appears as a deep-seated expansile asymmetric nodule involving the reticular dermis and subcutaneous fat. Usually, there is an abrupt transition from the benign blue naevus component to the nodule of melanoma. The nodule or nodules of melanoma show both architectural and cytological features of malignancy. The melanomatous component consists of sheets of cells that involve diffusely the deep dermis destroying the pre-existing structures with pushing margins and sharp demarcation between the neoplasm and adjacent dermis or subcutaneous tissue. Neoplastic melanocytes appear as large spindled to epithelioid cells with abundant cytoplasm and pleomorphic and hyperchromatic nuclei, with prominent nucleoli and frequent mitotic figures. Usually they contain little or no melanin. Without the associated benign component, these dermal nodules would be histopathologically indistinguishable from typical nodular or metastatic melanoma. Necrosis of individual cells as well as necrosis en masse may be also seen in the melanoma component, although this finding seems to be less
frequent than in melanomas arising de novo ("malignant blue naevus") (973). A perivascular inflammatory infiltrate, mostly composed of lymphocytes, which is usually lacking in blue naevus, is often seen around the melanoma arising in blue naevus.

Melanoma arising in the setting of blue naevus should be differentiated from the so-called atypical cellular blue naevus (118,2371). These lesions show clinicopathologic features intermediate between typical cellular blue naevus and malignant melanoma associated with blue naevus. The lesions show architectural atypia, characterized by asymmetry and infiltrative margins, as well as cytologic atypia, which consist of hypercellularity, nuclear pleomorphism, hyperchromasia, mitotic figures and necrosis. However, follow-up data of patients with atypical cellular blue naevus demonstrated that no patient experienced either a local recurrence or lymph node or visceral metastasis.

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

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

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

Metastatic spread

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

Immunoprofile

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

Electron microscopy

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

Somatic genetics

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

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

ICD-O code 8761/3

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

Epidemiology
About 1% of all infants have some kind of a congenital pigmented skin lesion (568). The giant congenital naevus (GCN) is estimated to occur in around 1 per 20,000 infants (67,411,1306). The risk of malignant transformation of a GCN has been estimated at from 5-20% but more recent studies based on statistical analyses suggest a figure of 6%. The GCN is a direct precursor of melanoma (1197, 1207,1927,2218). There is a bimodal distribution to the occurrence of melanoma in GCN. Most develop in childhood before the age of 10 (1508) with a second peak of incidence in adult life.

Sites of involvement
Malignant melanoma can occur anywhere in a giant congenital naevus. The lesion most commonly arises in lesions on the trunk but can appear in any area even in congenital naevi of the meninges (568,1306,1927).

Clinical features
The definition of GCN varies and includes a naevus with a diameter larger than 20 cm. Frequently large areas of the body (more than 2% of the body surface) are covered in a garment-like fashion (1306,1927). The trunk and head and neck are the most common sites for these naevic lesions. The melanoma, very rarely present at birth, usually appears as a rather rapidly growing asymmetrical nodule or plaque of blue-black, reddish or even rarely flesh colouration (568,1009). Melanoma can occasionally present as a cystic lesion. Therefore, any GCN that develops an apparent subcutaneous cyst must be biopsied. Melanoma is only one of many benign and malignant tumours that may occur in GCN (1009,1928).

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

Histopathology
Histologically, the tumours are often asymmetrical and sharply demarcated from the adjacent congenital naevus. If superficial, there is effacement of the rete ridges of the epidermis and often ulceration. The intraepidermal component usually is composed of epithelioid cells with pigmentation. Pagetoid spread is commonly noted. The tumour cells of the dermal component usually form expansile...
nODULES. They exhibit fully transformed malignant characteristics with very irregular chromatin patterns and prominent nucleoli. There is variable pigmentation. Both single cell and zonal necrosis may be observed. The melanoma cells as they abut or infiltrate as cords into the adjacent naevus show no evidence of maturation but maintain their fully malignant characteristics. Mitoses are common and atypical forms are usually present. A lymphocytic host response is often noted. Occasionally, a desmoplastic host response may be observed as well as focal mucinosis. In our experience, the vertical growth phase dermal nodules may exhibit prominent areas of different cell types with different degrees of pigmentation (568,703,1197,1928). Histologically, the presence of a residual dermal naevic component with congenital features may be quite difficult to find, particularly, if present in the wall of a vessel. The differential diagnosis includes the proliferative nodules that also arise in large congenital naevi.

**Somatic genetics**

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

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**Definition**

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

**Epidemiology**

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

**Localization**

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

**Clinical features**

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

Histopathology
The same histopathological criteria should be utilized for diagnosis as have been developed for adult melanomas (155, 159A, 417A, 1990A, 2232). However, clinical information must be strongly considered, particularly age, since cutaneous melanoma is almost nonexistent under the age of two years and especially in the neonatal period.

The important stimulants of melanoma must be excluded: 1) atypical nodular proliferations developing in congenital nevi in infants and young children and 2) Spitz naevi.

Great attention should be given to avoiding over diagnosis melanoma and at the same time to the under recognition of atypical and borderline lesions that require adequate surgery and follow-up for disease recrudescence. Lesions not clearly meeting sufficient criteria for melanoma should be designated as biologically indeterminate. Features appearing to be most useful for the distinction of melanomas from naevi are large size (i.e., >7 mm), ulceration, high mitotic rate (>4 mitoses/mm²), mitoses in the lower third of the lesion, asymmetry, poorly demarcated lateral borders, lack of maturation, finely-divided melanin, and marked nuclear pleomorphism (155, 159A, 2232). Melanomas in children can be (somewhat artificially) categorized into three principal groups (155, 159A, 2232).

Conventional melanomas
About 40 to 50% of melanomas in children are similar histologically to those in adults (159A, 2232). The intraepidermal components of such melanomas consequently may be pagetoid, lentiginous, or nested. Melanomas of glabrous skin are exceedingly rare in childhood (159A, 2232). Solar (so-called lentigo maligna) melanomas do not occur in childhood. However, melanomas diagnosed in patients with XP are histologically often similar to solar melanomas except that the actinic damage characteristic of adult tumors is absent (159A, 2232).

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

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

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

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

Pagetoid melanocytosis and lentiginous melanocytic proliferation and are features commonly observed in naevi developing in children, particularly in glabrous skin. These changes must not be overinterpreted unless architectural disorder is prominent and cytological abnormalities are present throughout the breadth of the lesion.

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

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

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

ICD-O code 8720/3

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

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

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

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

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

Table 2.06
Sex and ages in series of patients with naevoid melanomas.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of subjects</th>
<th>M/F Ratio</th>
<th>Mean Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNutt (1563)</td>
<td>5/16</td>
<td>2.2</td>
<td>M 47 (26-75); F 45 (44-57)</td>
</tr>
<tr>
<td>Schmoeckel (2092)</td>
<td>25/33</td>
<td>0.32</td>
<td>M 43 (22-52); F 49 (16-76)</td>
</tr>
<tr>
<td>Zembowicz (2596)</td>
<td>10/20</td>
<td>1</td>
<td>M 41 (19-61); F 44 (26-81)</td>
</tr>
<tr>
<td>Blessing 2000 (262)</td>
<td>10/14</td>
<td>0.4</td>
<td>48.6 (30-77) (small cell MM)</td>
</tr>
<tr>
<td>Blessing 1993 (261)</td>
<td>M &gt; F</td>
<td>57</td>
<td>( verrucous MM)</td>
</tr>
</tbody>
</table>

Fig. 2.34 Naevoid melanoma. A Naevoid melanoma, papular lesion. (A) At low magnification, note the lack of maturation and the lack of good naevus formation in the dermis. B Naevoid melanoma, papular lesion. (B) At intermediate magnification, many of the cells are hyperchromatic and atypical. C Naevoid melanoma, papular lesion. Perivascular infiltration is at the base of the lesion.
Naevoid melanoma can occupy a portion of a pre-existing intradermal or compound naevus. The melanomas have a relatively uniform population of small cells with hyperchromatic angulated nuclei or a population of medium-sized to large melanoma cells with more open nuclear chromatin and pale cytoplasm. Inflammatory reaction usually is slight and may be absent. The lesions often are dome-shaped, polypoid, or verrucous in profile (261,568,1562,1563,2092,2543, 2596).

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

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

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

Prognosis and predictive factors
Predictive features of naevoid melanoma prognosis are tumour thickness, mitotic rate, and large cell type. From 3,500 melanomas, Schmoeckel et al. (2092) selected naevoid melanomas with at least 5 years of follow-up unless there was earlier metastasis. Thirty-three cases were selected: 18 were disease free for at least 5 years. Fifteen had developed metastases. Eight had died of disseminated melanoma. The "most
important criterion was tumour thickness” (but mitoses also seem important): McNutt et al. (1562) studied 16 naevoid melanomas and observed that 2 died of melanoma (both large cell type), and one was alive with metastases (10 years, small cell type). Thirteen had wide excisions with no evidence of residual disease or were lost to follow-up. Zembowicz et al. (2596) selected 20 cases of naevoid melanomas from their files. Three had died and 6 had metastases. There was a three-year follow-up on 8 cases, with a mean follow-up period of 2 years. They conclude: “Naevoid melanoma, as currently defined in the literature and in the present study, seems to have a prognosis similar to that of classical melanoma.”

Wong et al. (2543) studied 7 cases of naevoid melanoma (two dome-shaped and five verrucous types) and found local recurrences in 3 and regional metastasis in one patient after 2 years, with a follow-up of 5 months to 5 years. Lohmann et al. (1444) studied 10 patients with diagnostically controversial lesions who underwent sentinel node biopsy. The differential diagnosis was between Spitz naevus and melanoma. In 5 of the 10 patients, there were sentinel node deposits of tumour in the parenchyma. All patients were alive and free of disease on follow-up of 10 to 54 months.

**Variants and differential diagnosis**

**Minimal deviation melanoma**
In the writings of Dr Richard Reed et al. (1911), this category was analogous to the minimal deviation hepatomas of experimental liver carcinogenesis, which were thought to deviate from the normal cells by only a single enzyme defect, and greatly resembled normal hepatocytes. Initially the minimal-deviation melanomas were characterized as having small cells, without much cytologic atypia, but they all had the architectural patterns of other melanomas. As this concept evolved, minimal deviation melanomas were divided into the following types: blue naevus type, Spitz naevus type, halo naevus type, borderline melanoma, as well as the ordinary minimal deviation melanomas. This created considerable confusion, particularly since the name “minimal deviation” implies a better prognosis, which has not been a consistent finding (2255). Naevoid melanoma as defined here was mixed into the various types of minimal deviation melanomas. As defined above, a diagnosis of naevoid melanoma requires both architectural and cytological mimicry of a naevus. Recently a subtype of small-cell naevoid melanoma has been described that develops predominantly in elderly individuals with sun-damaged skin (1313). This variant has an atypical lentiginous junctional melanocytic proliferation with a nested pattern that may be mistaken for a junctional naevus. This variant has a male predominance and the melanomas occur predominantly on the trunk. The epidemiology suggests that these junctional lesions may be precursors of lentigo maligna or superficial spreading melanomas.

**Small cell melanoma**
Melanomas composed of small cells have been studied separately by Kossard and Wilkinson in 1997 (1317). While some of them are naevoid melanomas, many have the architectural patterns of ordinary superficial spreading melanomas, lentigo maligna melanomas, and acral-lentiginous melanomas. In contrast, naevoid melanomas closely resemble a benign compound or intradermal naevus in architecture. They are all included in the original concept of minimal deviation melanoma. Confusion in terminology arises between small cell melanoma and what we define as naevoid melanoma. This confusion is due to the use of the terms “small naevoid cell type” in small cell melanomas, just on the basis of cell size and without restrictions on the architecture of the lesion. As defined above, a diagnosis of naevoid melanoma requires both architectural and cytological mimicry of a naevus.
melanoma in situ. This type of lesion needs further studies as to whether it represents a melanoma sui generis or a lesion with a high propensity to develop further mutations leading to melanoma. It does not fit into the current restricted definition of naevoid melanoma since it has a prominent junctional component and does not involve the dermis in the early stages.

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

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

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

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

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

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

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

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

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

Synonym
Local recurrence of melanoma.

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

Etiology
The etiological factors are those of the primary melanoma.

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

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

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

<table>
<thead>
<tr>
<th>Persistent melanoma</th>
<th>Metastatic melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidermal component</strong></td>
<td>Usually present, with or without a dermal component.</td>
</tr>
<tr>
<td><strong>Dermal growth pattern</strong></td>
<td>The full range of patterns associated with primary melanoma.</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Lymphocytic inflammation usually present.</td>
</tr>
<tr>
<td><strong>Vascular invasion</strong></td>
<td>Sometimes present.</td>
</tr>
<tr>
<td><strong>Mitotic rate</strong></td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Cell type</strong></td>
<td>The full range of cell types seen in primary melanoma, frequently including a mixture of cell types.</td>
</tr>
<tr>
<td><strong>Associated naevus</strong></td>
<td>Commonly present.</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Epidermal collarette</strong></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td>Frequently present in zones of regression and in desmoplasia.</td>
</tr>
<tr>
<td><strong>Scarring</strong></td>
<td>Present in the dermis and often also in the subcutis.</td>
</tr>
</tbody>
</table>

NOTE: 1. In cases of persistent melanoma, histological review of the primary excision confirms the presence of in-situ or invasive melanoma (or both) at a margin of excision. 2. The microscopic features of metastatic melanoma involving the scar of the primary excision are the same as those of metastatic melanoma at a site distant from the scar, with the additional feature of the scar at the site of the completely excised primary melanoma (573).
variably pigmented patch adjacent to or surrounding the scar of the primary excision site. In some cases there may also be nodule formation when there is persistent dermal invasion, especially of desmoplastic melanoma.

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

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

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

**Differential diagnosis**
Rarely, pigmentation of the epidermis or growth of a nodule at the site of previous excision of melanoma may be due to the coincidental growth of an entirely new and distinct tumour such as dermatofibroma or pigmented basal cell carcinoma. The most important differential diagnosis, however, lies between true persistence of incompletely excised primary melanoma and the other form of “local recurrence” due to metastatic melanoma. Metastatic melanoma in or adjacent to the primary excision scar usually presents as a rapidly growing papule or nodule without pigmentation of the underlying dermis, sometimes associated with

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**Fig. 2.38** Local melanoma metastasis. So-called “local recurrence” of melanoma in the scar at the excision site of a primary melanoma completely excised with a margin of 25mm.

**Fig. 2.39** Persistent melanoma. A Melanoma in-situ at the lateral margin of the excision of a primary melanoma. B “Local recurrence”, at the excision site two years later, showing invasive melanoma, extensive adjacent melanoma in-situ and dermal scarring.
multiple similar, rapidly growing lesions separate from the primary excision site. Histologically, metastases involving the scar present exactly the same features as cutaneous metastases at a distance from the scar (2573).

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

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

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

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

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

**ICD-O code** 8761/0

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

**Clinical features**
Congenital melanocytic naevi - superficial type are frequently observed. They can be found on any anatomic site and belong to the group of small congenital naevi with a diameter smaller than 1.5 cm.
On gross examination they vary from macules and papules to plaques and reveal different colours from light brown to black. The lesions are usually round or oval with a smooth or papillated surface. They may be hairy or hairless.

**Histopathology**
In the superficial type of CMN, dense diffuse infiltrates of small monomorphous melanocytes are found in the upper part of the dermis and the mid-portion of the reticular dermis. The melanocytes are frequently arranged in a band-like pattern and are disposed in single files between collagen bundles (“splaying of melanocytes”).
An important criterion for diagnosis is the presence of melanocytes along epithelial structures of adnexa and their angiocentric distribution. They may be found within sebaceous glands, vessels, nerves and in smooth muscles {1168,1531}. In the compound type of a congenital naevus – superficial type, nests of melanocytes are present in the epidermis, mostly at the dermo-epidermal junction. Melanomas are very rare in newborn and young infants (see chapter on childhood melanoma). Congenital melanocytic naevi, biopsied shortly after birth or in the first years of life can display atypical intraepidermal changes (pagetoid melanocytes arranged as solitary units and nests; single cells present in the upper layers of the epidermis) similar to those of melanoma in situ {1514}. This finding is more commonly found in giant congenital naevi than in small ones. The clues for diagnosis of this unusual change in a benign naevus are found in the dermis where the large, pale melanocytes merge with smaller ones that have the characteristic features of a congenital melanocytic naevus.

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

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

**Proliferative nodules in congenital melanocytic naevi**

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

**ICD-O code** 8762/1

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

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

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

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

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

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

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

**ICD-O code**
8780/0

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

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

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

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

In some instances, metastatic melanoma may mimic common blue naevus (354). Blue naevus may co-exists with other types of naevus (see combined naevus).

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

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

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

Mongolian spot

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

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

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

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

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

Naevus of Ito and Naevus of Ota

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

Synonyms
Naevus Ota: Oculodermal melanocytosis, Naevus fuscoceruleus ophthalmo-maxillaris.

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

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

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

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

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

Cellular blue naevus

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

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

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

Clinical features
Tumours are usually large, varying from 1 to several centimetres, and the colour varies from light blue-brown to dark blue. Lesions are asymptomatic and grow very slowly, presenting as a non-ulcerated firm nodule (1957,2336). Exceptional cases present as a large plaque (358). Rare tumours arising in the scalp have been described with invasion of the underlying bone (1596) and even the brain (854).

The epithelioid variant of blue naevus is very rare and has mainly been described in patients with Carney complex who usually present with multiple lesions (396,399). Sporadic lesions are usually solitary and may occur in genital skin (1117,1646,1736).

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

Histopathology
Low-power examination reveals a fairly characteristic picture with a dumbbell-shaped multinodular tumour occupying the reticular dermis and often extending into subcutaneous tissue. A junctional component is not usually found. Areas of pigmentation alternate with poorly pigmented areas and, in a minority of cases, pigment is very scanty (2595). Cellular areas tend to be more prominent towards the centre of the tumour, and the cellularity may be most marked where the neoplasm protrudes into the subcutis. The cellular areas may alternate with sclerotic or hypocellular areas. In most cases there are focal areas representing or simulating a common blue naevus. High power examination reveals bundles of oval or spindle-shaped cells with pale cytoplasm, alternating with bundles of deeply pigmented spindle-shaped cells. In addition, dendritic melanocytes and/or round, somewhat epithelioid melanocytes may be seen. Cytoplasmic melanin is coarse and granular, and nuclei are regular and vesicular, with a single small inconspicuous basophilic nucleolus.

Maturation with depth is not a feature. A frequent finding however, is the focal presence of elongated slender melanocytes resembling Schwann cells, indicative of neurotization as seen in ordinary naevi. Some tumours exhibit a focal alveolar growth pattern (1597) and desmoplasia is occasionally prominent (1599). Degenerative changes including haemorrhage, cystic change and fibrosis, are seen in some cases. Focal mild or prominent myxoid oedematous change may also be a feature (1598), and balloon cell change has been documented (1806). Occasional cases display a number of unusual features including mitotic figures (1/10 HPFs), focal necrosis, and/or nuclear pleomorphism or hyperchromatism. Such cases show some overlap with the malignant variant of CBN and have been described as atypical CBN (118,2371).

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

**Immunoprofile**

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

**Genetics**

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

**Prognosis and predictive factors**

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

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**Deep penetrating naevus**

**Definition**

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

**Synonym**

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

**Epidemiology**

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

**Localization**

DPN has a wide anatomical distribution with predilection for the face, upper trunk and proximal limbs.

**Clinical features**

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

**Histopathology**

Low power examination typically reveals a compound wedge-shaped deeply pigmented dermal and, very rarely, superficial subcutaneous tumour. The base of the lesion parallels the epidermis. The junctional component, which is usually present and may be subtle, consists of small round nests of ordinary naevus cells. In fact, in most cases, a superficial dermal component, representing an ordinary naevus, may be found and therefore these lesions may be regarded as combined naevi. Much less commonly, focal changes mimicking a Spitz naevus or a blue naevus are found. Tumour cells are arranged in nests or bundles and have a short spindle-shaped or, less commonly, round morphology. The cytoplasm contains

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**Fig. 2.48** Hypopigmented cellular blue naevus. **A** In some cases, melanin is almost completely absent. **B** Mucoid change may be prominent in some cases. **C** One of the melanocytes is much larger than the others. Some refer to such cases as 'atypical cellular blue naevus'. **D** Large melanocytes are present; some are multinucleated.

**Fig. 2.49** Cellular blue naevus. **A** This lesion has a central focus of cystic change. **B** The edge of the cystic area.
abundant melanin and nuclei are vesicular with frequent intranuclear inclusions and a single small basophilic nucleolus. Hyperchromatism and variation in nuclear size may be seen, but as a rule mitotic activity is low or absent (usually not more than 1 per section). The melanocytes follow the path of adnexal structures and blood vessels and there is frequent perineural extension. Maturation is not seen. Some tumours have the cytomorphology of DPN but are superficial and lack the deep penetrating component. Similar changes are seen in a common form of combined naevus.

**Prognosis and predictive factors**

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

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

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

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

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

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

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

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

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

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

<table>
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<tr>
<th>Table 2.09 The naevus components potentially occurring in combined naevus</th>
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<tr>
<td><strong>Common acquired naevi</strong></td>
</tr>
<tr>
<td>- junctional</td>
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<tr>
<td>- compound</td>
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<tr>
<td>- dermal</td>
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<tr>
<td><strong>Congenital naevi</strong></td>
</tr>
<tr>
<td>- junctional</td>
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<tr>
<td>- compound</td>
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<tr>
<td>- dermal</td>
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<tr>
<td><strong>Dysplastic naevi</strong></td>
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<tr>
<td>(naevi with architectural disorder and cytological atypia)</td>
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<tr>
<td>- junctional</td>
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<tr>
<td>- compound</td>
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<tr>
<td>- dermal</td>
</tr>
<tr>
<td><strong>Blue naevi</strong></td>
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<tr>
<td>- ordinary or common</td>
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<tr>
<td>- hypercellular</td>
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<tr>
<td>- cellular</td>
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<tr>
<td>- plaque</td>
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<tr>
<td>- epithelioid</td>
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<tr>
<td><strong>Spitz naevi</strong></td>
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<tr>
<td>- junctional</td>
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<tr>
<td>- compound</td>
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<tr>
<td>- dermal</td>
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<tr>
<td>- desmoplastic</td>
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<tr>
<td><strong>Deep penetrating naevi</strong></td>
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<tr>
<td>Plexiform pigmented spindle cell naevi</td>
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<tr>
<td>Naevi with dermal epithelioid cell components (clonal naevus)</td>
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<tr>
<td>- inverted type A naevus</td>
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<tr>
<td>- naevus with dermal nodules</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
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R.L. Barnhill
may vary from being minuscule to large lobular or digitate aggregates. The nuclei are usually comparable in size to the surrounding conventional naevus cells, or may be slightly enlarged round, oval, or elongated and uniform. On occasion the nuclei may show variable often slight to moderate atypia. Melanophages are also frequently associated with these pigmented foci. This pattern of combined naevus is also probably morphologically identical to that of deep-penetrating naevus and plexiform pigmented spindle cell naevus (158,164,537,2126).

Another common pattern is that of an ordinary naevus and blue naevus. The ordinary naevus component may be compound or dermal, often overlies or is adjacent to the blue naevus component, and commonly has a congenital pattern. The blue naevus elements most often consist of heavily-pigmented dendritic melanocytes, melanophages, and variable fibrosis. Less commonly, the spindle cells typical of cellular blue naevus may also be present with or without dendritic cells. The component of blue naevus may extend deeply into the reticular dermis as nests or fascicles, often in a plexiform configuration. Despite the two or more components, such naevi are usually symmetric, well-circumscribed, orderly, and display little or no cellular atypia. Spitz naevi uncommonly are observed in association with ordinary naevus elements (1961). The topographic relationships of these two components include the Spitz naevus component being adjacent to, beneath, or admixed with the common naevus elements. Such naevi also may have a desmoplastic stroma as in desmoplastic Spitz naevi.

After the above relatively well-recognized forms of combined naevus, almost any combination of cell types is possible (156,2116). Thus, one may encounter naevi containing various admixtures of ordinary naevus cells, dendritic melanocytes, Spitz naevus cells, and perhaps other transitional cell types. Atypical features may also be observed such as disordered patterns of melanocytes and cytological atypia of both the intraepidermal and dermal components.

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

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

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

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

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

Melanotic macules

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

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

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

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

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

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

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

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

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

Histopathology
Similar histopathologic changes can be demonstrated in all types of melanotic macules. There is usually no perceptible or a slight increase in the number of melanocytes, which are situated at the dermo-epidermal junction in solitary units. The melanocytes exhibit small and monomorphous nuclei and delicate dendrites. Using Fontana-Masson silver stain, the dendrites are better visible. Atypia is not observed. The basal layer reveals prominent hyperpigmentation. Occasionally hyperplasia of the epidermis can be seen. Melanophages and a mild inflammatory infiltrate are often present in the superficial dermis. Reticulated melanotic macules show marked hyperpigmentation of the epidermis especially at the tips of the rete ridges whereas the suprapapillary plates are spared and nearly devoid of melanin. A slightly increased number of finely dendritic melanocytes can be observed in the lower layers of the epidermis. In contrast, solar lentigo represents an evolving seborrhoeic keratosis revealing small buds or nubbins of hyperpigmented keratinocytes.

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

Fig. 2.53 Melanotic macule on the lip. A Brown-black macule with irregular margins on the lower lip. B Pigmentation of the epithelial basal layer and melanophages in the papillary dermis.
Differential diagnosis

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

**Simple lentigo – lentiginous melanocytic naevus**

**Definition**

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

**Synonyms**

Lentigo simplex, naevus incipiens.

**Clinical features**

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

**Histopathology**

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

**Prognosis and predictive factors**

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

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

ICD-O code 8727/0

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

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

In a recent survey by the American Academy of Dermatology, 98% of respondents recognized the dysplastic naevus as a distinct entity {2373}.

Epidemiology
The estimated total number of individuals affected by the familial form is approximately 32 000 in the United States {1320}.

Sporadic, histologically dysplastic naevi are seen in up to 50% of White adults, depending on how the lesion is defined. (535,571,1828). The estimated prevalences of dysplasia in a population based series of naevi ranged from 7-32% {1829}. The prevalence of clinically defined dysplastic naevi also varies according to the criteria used, ranging from 5–20%.

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

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

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

Diagnostic criteria
The Dutch Working Group produced five...
Melanocytic tumours

Dermoscopy and imaging

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

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

Progression to malignant melanoma

Although melanomas in patients with dysplastic naevi may arise within preexisting dysplastic naevi, the vast majority arise de novo. Histologic changes indistinguishable from those of dysplastic naevi are often observed at the peripheries of primary melanomas not associated with naevi and such findings have been interpreted as representing "precursor" dysplastic naevi (672). Dysplastic naevi may have chromosomal instability and poor repair mechanisms after sunlight induced injury (1067, 2128). Landi et al demonstrated an increased relative risk for melanoma in a dysplastic naevus group with poor in vitro DNA repair capacity (1360). Elder classified 6 stages of tumour progression via monoclonal antibodies to melanoma cells or their extracts on frozen tissue sections (675A).

Histopathology

Definition and description

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

There is lack of consensus regarding the histologic classification of dysplastic naevi. Historically, some groups advocate that atypical architecture is all that is required to establish the diagnosis (1943, 1980), while others require cytological abnormalities (1925). Shea et al recommend evaluating both cytology and architecture in the diagnosis of DN (2158). More recent descriptions of features common in DN histology included a central dermal naevocytic component with a peripheral extension of a junctional component, elongated epidermal rete ridges, bridging of nests of melanocytes at the dermo-epidermal junction, nests of melanocytes at the sides of rete ridges as well as at their bases, and concentric eosinophilic papillary dermal lamellar fibrosis (1943). Ackerman and others have placed emphasis on the "shoulder phenomenon" which describes peripheral extension of the junctional component beyond the dermal component in dysplastic naivei (18, 1828). In general, histologic criteria involving architecture used to describe dysplastic naevi include: circumscription, symmetry, cohesion, suprabasalar melanocytes, confluence and single cell proliferation. Cytologic features include: nuclear shape and staining, nuclear size, nucleolar prominence, and cell size (2158). One of the problems in the definition of these lesions is that the histologic changes are non-specific and may be seen in a number of other naevi without clinical features of "dysplastic" naevi such as growing naevi in children and naevi located on certain anatomic sites such as the scalp and flexural areas. Furthermore, the definitions used to describe cytologic atypia are subjective.
Dysplastic naevus

as in no case are the atypical cytologic features as frankly atypical as seen in fully developed melanoma.

**Immunoprofile**

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

**Growth fraction / MIB-1 index**

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

**Electron microscopy**

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

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

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

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

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

Somatic genetics
Cytogenetics and CGH
Jaspers et al performed cytogenetic investigations on lymphocytes and fibroblasts from 25 individuals with dysplastic naevus syndrome and compared the results with a a control population of clinically normal relatives and unrelated individuals. In five DNS patients, increased frequencies of cells with random chromosomal rearrangements including translocations and inversions were observed. These abnormalities were absent in the control population (1134).

Caporaso analyzed the karyotypes of 163 family members from 13 melanoma-prone families to investigate whether chromosomal instability contributes to familial melanoma. Cutaneous malignant melanoma and dysplastic naevi syndrome patients each had increased structural and numerical abnormalities compared with pooled controls (377). However, the criteria used to define lesions as "dysplastic" naevi were subjective from the outset so the validity of such studies remains in question.

Park and Vortmeyer examined the frequency of p16 and p53 deletion in nine dysplastic naevi and 13 benign intradermal naevi with five microsatellite markers. Hemizygous deletion was detected in seven of nine dysplastic naevi at one or more loci for p16. No loss of heterozygosity was detected in any of the benign intradermal naevi (1775).

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

**Genetic susceptibility**

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

**Prognosis and predictive factors**

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

**Number of dysplastic naevi and family history**

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

**Histopathological criteria**

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

**Genetic predictive factors**

Currently, there are no commercially available genetic tests that would be predictive of dysplastic naevi progression to melanoma.
Site specific and Meyerson naevi

H. Kamino
D. Weedon

In some anatomic sites, naevi may have atypical histological features. This chapter discusses three clinicopathologic entities: acral, genital and Meyerson naevi, but other site specific features have been described, including naevi occurring in flexures, umbilicus, ear and scalp.

**Acral naevus**

**Definition**

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

**Synonyms**

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

**Epidemiology**

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

**Localization**

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

**Clinical features**

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

**Etiology**

The origin of AN is hypothesized to involve repeated trauma {701,2181,2182}, foci of “unstable” melanocytes {1416} and racially-correlated variations in melanosome aggregation {1612}.

**Histopathology**

Distinction of acral naevi from melanoma can be difficult because both may be asymmetric, poorly circumscribed and have intraepidermal ascent of cells (292,701,984,1545,2181,2182). Suprabasal melanocytes in AN are relatively more columnar, circumscript and less voluminous than in melanomas {1246}. Signoretti et-al. have shown that symmetry, circumscription, the columnar organization of ascending melanocytes and organization of the junctional component are all influenced by the histologic plane of section; to wit, naevi sectioned perpendicular to dermal glyphics are more likely to have benign attributes {2017,2018}. Subsequently, severe melanocytic atypia and a dense lymphocytic infiltrate have been found the most reliable features indicative of melanoma (493,707).

**Genital naevus**

**Definition**

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

**Synonyms**

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

**Epidemiology**

About 10% of men and women have pigmented genital lesions {574,784,1955}, but many are lentigines {784,1955}. Histologically confirmed GN occur in 2% of women {267,480,1955}. AMNGT comprise a minority of all GN {267,480,1955}. They typically present by the twenties {1608} and, in contrast to vulvar melanoma, are seen exclusively in premenopausal women {1608,2015}. Dysplastic naevi may also occur on the genitalia but they are usually observed in people with dysplastic naevi elsewhere on their bodies {267,1608}. Vulvar naevi were said to have increased premalignant potential {1763}, though recent data

![Fig. 2.60 Acral naevus. A Epiluminescence microscopy of an acral naevus demonstrating linear hyperpigmentation within the furrows of dermal glyphics. B Intraepidermal melanocytes with short dendrites are seen along and above the basal layer.](image-url)
Site specific and Meyerson naevi

refutes this (1954). Histological studies suggest that from 1% (391) to 12% (495) of vulvar melanomas are associated with a naevus.

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

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

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

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

Meyerson naevus

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

Synonyms and historical annotation
"Spongiotic change in melanocytic naevi" (2478), halo dermatitis (352,2330), halo eczema (1329) and perinaevic eczema (1816).

The eponym “Meyerson naevus” (MN) was suggested (1706) to honour the 1971 description of a spongiotic dermatitis involving melanocytic naevi (1595).

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

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

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

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

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

**Immunoprofile**

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

Fig. 2.63 Meyerson naevus. Spongiosis, parakeratosis and irregular acanthosis characterize the epidermis.
Persistent (recurrent) melanocytic naevus

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

Synonym
Pseudomelanoma (1310)

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

Histopathology
Scanning magnification shows commonly above a dermal melanocytic naevus a scar with fibrosis. The intraepidermal changes are characterized by sharp circumscription and confluent nests of melanocytes, that are not equidistant and vary in sizes and shapes. The nests are mostly situated at the dermo-epidermal junction. Melanocytes are also arranged as solitary units at the dermo-epidermal junction and sometimes above it in upper layers of the epidermis (1037).

Assessment of the original specimen is very important for an accurate diagnosis to ensure that the lesion is really a persistent melanocytic naevus and not a persistent melanoma.

Differential diagnosis
The features within the epidermis and in epithelial structures of adnexa may simulate a melanoma in situ. However, the sharp circumscription of the intraepidermal component, the presence of melanocytes in nests and as single units mostly at the junction and the typical naevoid cells of the preexisting dermal melanocytic naevus beneath a scar are helpful clues to the diagnosis of persistence (recurrence). Furthermore in persistent melanocytic naevi the melanocytic proliferation within the epidermis is confined to the area above the scar.

Fig. 2.64 Persistent (recurrent) melanocytic naevus. A Small irregular black macule. A scar surrounds the lesion. B Persistent (recurrent) melanocytic naevus. Melanocytes are arranged as solitary units along the dermo-epidermal junction and also above it. Atypical nuclei can be observed. Note involvement of the follicle.

Fig. 2.65 Persistent (recurrent) melanocytic naevus. Trizonal arrangement: 1) Dermal melanocytic naevus. 2) Above the melanocytic naevus a scar revealing fibrosis. 3) Intraepidermal changes with nests of melanocytes with irregular shapes and a tendency to confluence at the dermo-epidermal junction.
Spitz naevus

Definition
Spitz naevus is a benign proliferation of large spindled, oval or large round (epithelioid) melanocytes that begins in the epidermis, and evolves into compound or intradermal stages. This distinguishes it from some forms of blue naevus, in which the lesion is wholly intradermal from the outset.

ICD code 8770/0

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

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

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

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

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

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

Histopathology
Because the findings of Spitz naevus differ significantly at various stages, we will describe those in detail. Spitz naevus begins as a proliferation of large oval melanocytes at the dermal-epidermal junction. This can occur along a front of only a few mm., and is first recognizable by single, large melanocytes with abundant eosinophilic cytoplasm and large vesicular nuclei. There are often a large number of cells with several nuclei, even in small lesions. Cytoplasm is abundant, and even though the nuclei may be large, they are usually monomorphous. Clefts demarcate the melanocytes from adjacent keratinocytes. Even if single cells are present in number above the junction, they are evenly distributed (355). As these lesions enlarge, the epidermis above the proliferation thickens, and nests begin to form. The epidermal thickening is largely via hyperplasia of the spinous layer, with squamatization of the basal layer and pointed rete ridges.
There is corresponding hypergranulosis and compact hyperkeratosis. Within the junctional nests of a Spitz naevus are clefts, separating the melanocytes from one another, and from the epidermis. The clefts tend to be prominent over the apices of junctional nests. The nests may appear to be embedded in the epidermis, rather than lying at the bases of rete ridges. The epidermal hyperplasia of a well developed junctional Spitz naevus, and the nests of the naevus itself are both well circumscribed {19,1636, 1638,1769,2479}. By the time that nests are of substantial size, one may encounter Kamino bodies in the epidermis. Kamino bodies are dull pink staining globules, up to the size of several keratinocytes, often with a scalloped border and a periphery in which there are crescent shaped, compressed appearing keratinocytes (1186). Unlike dyskeratotic cells, which are more brightly eosinophilic, their major ingredient is basement membrane material. They stain with PAS-D and with immunoperoxidase stains for basement membrane components, such as laminin and type IV collagen (2499).

Compound Spitz naevus forms when junctional nests become incorporated into the dermis. In early compound lesions, one may see a dense lymphocytic infiltrate, rather than the sparse perivascular one that most authors describe. The dermal nests tend to be smaller than the junctional ones, and as melanocytes descend into the reticular dermis, one can discern a gradient from large nests to smaller ones, and single cells may predominate at the base. Mitotic figures can be present in the upper part of a compound Spitz naevus, but tend to decrease in number toward the base of the lesion. Maturation of melanocytes is also a correlate, with smaller cells that have less cytoplasm, smaller nuclei, and smaller and less eosinophilic nucleoli all findings that reassure the pathologist. If a Spitz naevus is pigmented, the pigmentation lessens in the lower half of the lesion. When this is prominent, some apply the term desmoplastic Spitz naevus. Unlike the case in desmoplastic melanoma, there are no markedly elongated fascicles of cells. If the proliferation abuts the subcutis, one may see lymphoid nodules. For both compound and intradermal lesions, an important finding is that the nests at each level of the lesion should be similar in size, with the cells similar in overall and nuclear size and in pigmentation.

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

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

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

![Image](Fig. 2.67 Spitz naevus, junctional type, Clefts separate melanocytes from one another. Several large Kamino bodies are present.)
found from early childhood to young adulthood in which there are some features of Spitz naevus and others of melanoma. Common denominators include a vertical orientation, extension into the subcutis with no diminution in cellularity and a blunt, multinodular interface, ulceration, a plasmacytic infiltrate and deep mitotic figures. Such cases have been described as “malignant Spitz naevus” and also simply regarded as melanomas (2205). In the initial study of “malignant Spitz naevus” there were 3/32 lesions in which palpable lymph node enlargement had occurred, and another 3 in which lymph node involvement was detected on elective dissection. Very similar lesions have been described as melanomas in children (1632). Follow up data has been presented to the effect that systemic metastasis may not occur, or may be much less frequent than in adults with conventional melanomas matched for thickness. Clearly, further studies are needed to determine if these lesions are fundamentally Spitz naevus, melanoma, or neither.

**Somatic genetics**

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

**Definition**

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

**ICD-O code**

8770/0

**Synonyms and annotation**

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

**Epidemiology**

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

**Clinical features**

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

**Histopathology**

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

**Prognosis and predictive factors**

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

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

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

ICD-O code 8723/0

Synonyms
Sutton naevus; leukoderma acquisitum centrifugum (2297).

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

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

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

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

**Differential diagnosis**

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

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

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

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**Fig. 2.73 Halo naevus.** A Infiltrating lymphocytes are intimately admixed with naevus cells, which will lead to apoptosis and ultimate disappearance of the naevus cells. In later examples, naevus cells are more inconspicuous than they are in this field. B Extending 1 to 2 mm beyond the lateral border of the dermal naevus component, the papillary dermis is widened with slight fibroplasia, there is a patchy lymphocytic infiltrate, and there is absence of pigment and of melanocytes in the overlying epidermis. This region constitutes the clinical halo. C Normal skin adjacent to the halo shows a normal papillary dermis, normal melanin pigment in basal keratinocytes, and the presence of melanocytes, which can be demonstrated if desired with a Melan-A stain.