CHAPTER 6

Neural Tumours

Cutaneous neural tumours represent a small but important part of the cutaneous soft tissue neoplasms. Their histogenesis is conceptually analogous to their deep soft tissue or visceral counterpart, i.e., they recapitulate to variable extent the architectural and cytologic constituents of normal peripheral or autonomic nerves. Likewise, their classification is identical to their soft tissue counterparts. In this chapter, only those tumours are discussed which are particularly relevant for the dermatopathologist by their distinct morphology, predominant cutaneous manifestation, or their recent recognition and significance in the cutaneous pathology. These include the neuroendocrine carcinomas, rare but problematic peripheral variants of primitive neuroectodermal tumours, the non-neoplastic neuroma group with its spontaneous and reactive types and the recently defined, but still histogenetically controversial, nerve sheath myxoma-neurothekeoma spectrum.
### WHO histological classification of neural tumours

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<th>Tumour</th>
<th>Morphology Code</th>
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<td>Primitive neuroectodermal tumour (PNET)</td>
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<td>Ewing sarcoma</td>
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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) [786] and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

### TNM classification of skin (Merkel cell) carcinomas

#### TNM classification

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

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

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

#### Stage grouping

<table>
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<td>T4</td>
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<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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</tbody>
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Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

1. For PNET and Ewing sarcoma see TNM table of soft tissue tumours
2. [894,2219].
3. A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.
**Palisaded, encapsulated neuroma and traumatic neuroma**

**Definition**
Palisaded, encapsulated neuroma (PEN) is considered a spontaneous proliferation of nerve fibres without evidence of previous trauma.

**Synonyms**
Solitary circumscribed neuroma, spontaneous neuroma, true neuroma

**Historical annotation**
The tumour was described by Reed et al. in 1972, who pointed out that despite the occasional nuclear palisading and encapsulation, the tumour is different from Schwannoma (1908).

**Epidemiology**
PEN is most common in the 5th and 7th decades and occurs in an approximately equal ratio in both genders. The majority of the lesions, about 90%, are located on the face, but they can occur anywhere on the body. Mucosal involvement has also been recorded (453,752,1908).

**Clinical features**
PEN usually manifests as a solitary, small (2-6 cm), skin-coloured or pink, firm or rubbery, dome-shaped, asymptomatic papule or nodule. There is no established association with neurofibromatosis (453,752,1908).

**Macroscopy**
On cut sections, the tumour is a yellow-pink, firm ovoid mass in the dermis.

**Histopathology**
On low magnification, PEN is a well-circumscribed, round or oblong nodule located in the dermis. It is surrounded by a thin fibrous capsule, which is poorly discernible or incomplete near to the epidermal aspect of the tumour. The tumour is composed of tightly woven fascicles which are separated by cleft-like spaces. The proliferating cells are slender spindle cells with ovoid, evenly chromatic nuclei and eosinophilic cytoplasm. A parallel arrangement of nuclei resembling a palisading pattern or rudimentary Verocay bodies is occasionally present. The proliferating cells are slender spindle cells with ovoid, evenly chromatic nuclei and eosinophilic cytoplasm. Mitotic figures are rare or absent. PEN lacks distinct fibrosis, inflammation or granulomatous reaction. A connection with the originating nerve usually requires serial sectioning of the tissue. Silver impregnation reveals numerous nerve fibres (axons), usually in parallel arrangement with the longitudinal axes of the fascicles (55,80,90,453,585,646,752,1314,1908).

**Immunophenotype**
The cells in the capsule stain for epithelial membrane antigen, whereas the spindle cells of the fascicles are positive for S-100 protein and collagen type IV. The axons are labeled with antibodies to neural filaments. Variable myelinization is detected by CD57 (Leu-7) and myelin basic protein (55,80,90).

**Variants**
**Plexiform and multinodular types.**
These rare variants represent unusual growth pattern, but otherwise they retain the usual internal structures and composition of PEN (81,84).

**Spontaneous, non-encapsulated neuromas**
These tumours are part of the Multiple Mucosal Neuroma (MMN) syndrome, which is often part of the Multiple Endocrine Neoplasia syndrome (MEN2b), which is associated with pheochromocytoma and medullary carcinoma of the thyroid (815). The neuromas in MMN manifest as numerous, soft-rubbery, skin-coloured or pink papules and nodules around mucosal orifices, lip, eyelids, and tongue, but scattered cutaneous involvement can also occur (835,1658,1994). Musculoskeletal abnormalities and intestinal ganglioneuromato-

![Fig. 6.1 Palisaded, encapsulated neuroma. A Multinodular variant of palisaded encapsulated neuroma. B The tumour is formed by compactly arranged fascicles separated by artificial clefts.](image-url)
sis are also part of the syndrome (236,2504). Histologically, the tumour is composed of numerous tortuous or fascicular arrangements of hyperplastic nerve bundles infiltrating the submucosa or the dermis, hence the term “non-encapsulated neuroma” has also been applied. The individual fascicles have a linear, elongated appearance instead of the round or oblong structure of PEN; however, the constituent cells are identical to those seen in PEN. Occasionally perineurial and endoneurial increase of mucin can be noted. The immunohistochemical profile of this variant is similar to PEN (815, 835,1658,1994).

Genetics
Activated mutations of the RET proto-oncogene, involving the somatic or the germline cell-lineage are found in both the inherited and acquired forms (466, 545,2310). However, MMN without genetic abnormalities have also been reported (1863,2379).

Prognostic factors
PEN and its variants are benign, and simple excision is a sufficient treatment. The mucosal neuromas of MEN2b often precede the manifestation of the other endocrine tumours. Therefore their correct recognition is important (1020).

Traumatic neuroma

Definition
Traumatic neuromas represent reactive or regenerative proliferation of the nerve sheath components as an attempt to reestablish lost nerve integrity after sharp or blunt physical trauma.

Synonyms
Amputation neuroma, supernumerary digit

Epidemiology
Traumatic neuromas can occur at any age or gender. The amputation type is more common on the extremities (1535). A special variant sometimes referred to incorrectly as “supernumerary digit” occurs on the lateral aspects of hands or feet of newborns. They represent amputation neuromas at the site of the in-utero separated extraneous digit (487,2152).

Clinical features
Traumatic neuromas develop at the sites of previous trauma usually as solitary, skin-coloured, broad-based, firm papules and nodules. They are often sensitive or painful on pressure. Lancinating pain is characteristic of amputation neuromas (351,530,2342).

Macroscopy
Traumatic neuromas are firm, white-yellow, ill-defined dermal or subcutaneous masses often in a discernible association with the proximal nerve stump.

Histopathology
The tumour is composed of an irregular, haphazardly arranged proliferation of regenerating nerve fascicles of various sizes and shapes embedded in a fibrous stroma. Earlier lesions show acute and chronic inflammation, occasional granulomatous inflammation, whereas more established lesions are markedly fibrotic. Although the tumour is encased in the sclerotic stroma, there is no true encapsulation, and the distal end of the regenerating nerve fascicles often infiltrates the stroma (90,2084). The individual nerve fascicles appear to recapitulate the architecture of the normal nerve fascicles, but there is considerable variation in their diameter. The constituent cells...
Palisaded, encapsulated neuroma and traumatic neuroma

are slender spindle cells (Schwann cells, perineurial cells, and endoneurial fibroblasts). Silver impregnation reveals numerous nerve fibres (axons) in the tumour in a pattern approximating the normal 1:1 ratio of Schwann cells and axons. The “supernumerary digit” is a polypoid lesion covered by thick hyperorthokeratosis with a fibrous stalk containing regenerating nerve fascicles. The morphology of the regenerating nerve fibres is identical to the ones seen in other amputation neuromas.

**Immunohistochemistry**

The constituent spindle cells of the nerve fascicles are positive for S-100 protein, collagen type IV, whereas the surrounding perineurial cells, when present, stain for epithelial membrane antigen. Antibodies to neural filaments highlight the axons, and myelinization can be demonstrated by antibodies to myelin basic protein and CD57 (Leu-7).

**Prognostic factors**

Traumatic neuroma is a reactive lesion, however it can cause local interference with adjacent organs and is often symptomatic. The usual treatment is simple excision.

![Fig. 6.4 Traumatic neuroma. A Supernumerary digit (amputation neuroma). Acral polypoid lesion with proliferation of nerve fascicles at the base of stalk. B Higher magnification of the regenerating nerve fascicles in the fibrous stroma. C The regenerating nerve fascicles show variation of diameter and orientation. The clear spaces correspond to increased perineurial mucin.](image)
Primary malignant peripheral primitive neuroectodermal tumour (PNET) / Extraskeletal Ewing sarcoma (ES)

Definition
PNET/ES are malignant small blue round cell tumours, which exhibit varying degrees of neuroectodermal differentiation. In the past, they were regarded as separate entities, but recent cytogenetic and molecular genetic studies have proven that they represent two ends of a phenotypic spectrum of the same tumour type – Ewing sarcoma being relatively undifferentiated and PNET showing morphological (light microscopic/ultrastructural) and/or immunohistochemical features of neuroectodermal differentiation.

ICD-O codes
PNET 9364/3
Ewing sarcoma 9260/3

Synonyms
Peripheral neuroepithelioma, peripheral neuroblastoma

Epidemiology
Primary PNET/ES of skin and subcutaneous tissue are rare neoplasms. These tumours are mainly seen in children and young adults (median age 18 yrs), but they occasionally afflict elderly individuals. There is no significant sex predilection (72,82,138,449,978,1389,1791,1815,2050,2146,2210,2295,2328,2416).

Etiology
The etiology of this tumour is unknown.

Localization
These neoplasms have been described on the scalp, face, neck, shoulder, trunk and extremities.

Clinical features
The tumours usually present as ulcerated or non-ulcerated, often painless, but rarely tender, nodules. Occasionally, they appear polypoid (138,978). Not infrequently, they are clinically misdiagnosed as benign tumours or cysts. A case of cutaneous PNET with numerous tumour nodules that were present for several years has been documented (2050).

Macroscopic features
The tumours are greyish white and fleshy. Foci of haemorrhage are sometimes noted. Their sizes usually vary from 5 cm to 10 cm.

Histopathology
The tumours usually occupy the dermis with focal extension into subcutis. Some tumours are entirely subcutaneous in location. The overlying epidermis may become ulcerated. The margins may be pushing or infiltrative. The neoplastic cells are small, round to oval and contain hyperchromatic or vesicular nuclei and scanty pale eosinophilic or vacuolated cytoplasm with ill-defined borders. The nucleoli are indistinct or absent. The cells are arranged in sheets, lobules, nests and trabeculae. The mitotic activity and necrosis vary from case to case. Many dark apoptotic cells may be seen. Prominent fibrovascular septa are present in most lesions and some exhibit peritheliomatous or pseudopapillary arrangement of cells. Occasionally, the stromal blood vessels form glomeruloid tufts with prominent endothelial and myointimal cells. Microcystic, pseudoglandular and pseudovascular spaces are observed in many neoplasms. Homer Wright rosettes and neuropil are only rarely present. In atypical examples of this tumour, larger cells with prominent nucleoli, pleomorphic cells with irregular nuclei or groups of mononuclear or binucleate rhabdoid or plasmacytoid cells are seen. Prominent epidermal inclusion cysts within the tumour have been described in one case. Intracytoplasmic glycogen can be demonstrated in most cases. The reticulin stain reveals fibrils around groups of tumour cells. The differential diagnosis of this neoplasm includes deposits of lymphoma/leukaemia, Merkel cell carcinoma, metastatic small cell neuroendocrine carcinoma, metastatic neuroblastoma, primary or metastatic rhabdomyosarcoma, glomus tumour, small cell melanoma and rare types of sweat gland tumour such as eccrine spiradenoma and non-neuroendocrine small cell carcinoma. Attention to histological detail, immunohistochemistry, EM studies and genetic analysis help to reach the right diagnosis.

Immunohistochemistry
Characteristically, the neoplastic cells exhibit positivity for CD99 (MIC2 gene product), β2 microglobulin, FLI-1 gene product, vimentin and one or more puta-
tive neural/neuroendocrine markers such as NSE, PGP 9.5, neurofilament proteins, synaptophysin and Leu-7. Usually the stain for chromogranin is negative. The CD99 positivity is usually strong, diffuse and membranous. The FLI-1 stains the nuclei of the neoplastic cells. Aberrant cytokeratin, desmin, GFAP, S100 protein and NKIC3 expression may be noted in scattered cells in some cases. The tumour cells are negative for LCA, B&T cell markers, myeloperoxidase, muscle specific actin, MYO-D1, myogenin, EMA and HMB 45 (138).

**Electron microscopy**
At the Ewing end of the spectrum, the cells appear rather non-descript with round nuclei and scanty organelles. There is usually abundant glycogen. The PNETs show elongated interdigitating cytoplasmic processes with a few rudimentary junctions, intermediate filaments, microtubules and sparse membrane bound dense core neurosecretory granules (100-250 nm in diameter). No myofilaments, desmosomes or melanosomes are seen (138).

**Genetics**
Around 90% of skeletal and extraskeletal PNET/ES exhibit a characteristic chromosomal translocation, t(11;22)(q24;q12). This results in the fusion of EWS gene on chromosome 22q12 with FLI-1 gene on chromosome 11q24. A small number of cutaneous cases have been subjected to cytogenetic/genetic studies and these have also demonstrated the typical genetic defects (978,1389). An additional copy of chromosome 22 was detected in one case. Conventional cytogenetic study, FISH and RT-PCR techniques have been used to detect these abnormalities.

**Prognosis and predictive factors**
These neoplasms are aggressive with metastatic potential. The usual sites of metastasis are regional lymph nodes, lung, liver and bones. However, the cutaneous PNET/ES appear to have a better prognosis than their soft tissue counterparts, probably because they are detected early and can be resected adequately. Long term survival has been recorded in a few cases with or without radiotherapy and adjuvant combination chemotherapy (138,478,978,2328). A prognostically relevant grading or staging system is not yet available for these neoplasms.
Nerve sheath myxoma / neurothekeoma

Z.B. Argenyi

Definition
These tumours encompass a spectrum of neuromesenchymal neoplasms characterized by proliferation of nerve sheath cells in a variable myxomatous stroma. They can be further classified into “classic” and “cellular” types.

ICD-O code 9562/0

Synonyms
Cellular neurothekeoma (used exclusively for the cellular variant), cutaneous lobular neuromyxoma, myxomatous perineuroma

Epidemiology
These tumours are rare. The "classic type" has been reported in middle-aged adults (mean 48.4), with predominance in females, of the head and neck areas and upper extremities (73,1865). The "cellular type" has been observed in younger adults (mean 24 yrs), more common in females, predominantly on the head and neck areas (88,99,161,371). However, both types can occur at any age and at any location (229,418,479, 1222,1674,1684,2355).

Clinical features
The “classic types” manifest as skin-coloured, pink, soft, rubbery papules and nodules, whereas the “cellular types” have a firmer, rather red-tan-brown appearance. Their size ranges between 0.5–2.0 cm. Both types are commonly asymptomatic, but may become sensitive or tender (73,88,99, 161,371,1865).

Histopathology
The “classic type” is usually a well-defined, multilobular or fascicular tumour located in the dermis with or without extension to the subcutis. The lobules contain abundant myxomatous stroma, which appear to be confined by a thin fibrous encapsulation. The mucin is connective tissue type acidic mucopolysaccharide and stains strongly with colloidal iron, which clears after hyaluronidase treatment. Within the mucinous stroma, there are sparsely distributed spindle, stellate, and polygonal cells without appreciable cytologic atypia. Mitotic figures are rare or absent (73,88,755,1865). The “cellular variant” shows an ill-defined, often infiltrative growth pattern involving the dermis and subcutis. The proliferating cells form fascicles and nests and are arranged in a plexiform or multilobular pattern. The constituent cells are mainly epithelioid type with ample eosinophilic cytoplasm and indistinct cytoplasmic membranes. The cells have large “bubbly nuclei” with prominent nucleoli. In a smaller percentage of the cases, the tumour is composed of spindle cells with plump or ovoid nuclei forming nests and whorls. In the “cellular type”, cytologic and nuclear atypia are more common and mitotic figures can be conspicuous. Myxoid material is usually scant or present only around the individual nests (88,99,161,371). In both the “classic” and “cellular types”, associated stromal changes, such as fibrosis, hyalinization of the collagen, patchy chronic inflammation, and angioplasia can occur. Changes showing transition between the “classic” and “cellular types” within the same lesion have been documented. A direct connection with nerve twigs can be demonstrated only rarely.

Immunohistochemistry
The stromal cells in the “classic” type stains strongly for S-100 protein, collagen type IV and weakly for neuron-specific enolase and CD57 (Leu-7). The capsule, when present, may label for epithelial membrane antigen. The “cellular” type does not have a specific or consistent phenotype. The cells show variable expression of PGP9.5, collagen type IV, NK1/C3, CD34, and occasionally smooth muscle specific actin and CD57 (Leu-7). Staining for S-100 protein is rare, and

Fig. 6.7 Nerve sheath myxoma (neurothekeoma). A Cellular neurothekeoma (cellular variant of nerve sheath myxoma). The tumour cells form nests and strands infiltrating the dermis. B Nerve sheath myxoma "classical type". Lobular and fascicular dermal proliferation with myxomatous stroma.
when present it is usually in lesions where there are elements of the “classical” type (87,88,99,161,371,798,1370,2281,2454).

**Prognosis**
Both variants are considered benign tumours, although rare cases of the “cellular” type with concerning cytologic atypia and mitotic activity have been reported (231,357). Both tumours can recur after incomplete removal; therefore, a complete excision is recommended for treatment.

Fig. 6.8 Nerve sheath myxoma (neurothekeoma). **A** Higher magnification of the lobules shows the mixture of variable cellularity and myxomatous changes. **B** The tumour nests are well defined, but not encapsulated and contain minimal or no mucin. The adjacent stroma is hyalinized. **C** Stellate, polygonal, and spindled cells are embedded in a markedly mucinous matrix.
Merkel cell carcinoma

Definition
Merkel cell carcinoma is a rare malignant primary cutaneous neoplasm with epithelial and neuroendocrine differentiation. Tumour cells share morphologic, immunohistochemical and ultrastructural features with Merkel cells, but a direct histogenetic link is unproven.

ICD-O code 8247/3

Synonyms
First described in 1972 by Cyril Toker as trabecular carcinoma (2357). Other synonyms include neuroendocrine carcinoma of the skin, primary small-cell carcinoma of the skin, and cutaneous APUDoma.

Epidemiology
The estimated incidence of Merkel cell carcinoma is about 470 new cases per year in the United States. The tumour most commonly affects Caucasians (0.23 annual age adjusted incidence per 100,000) and is exceptionally rare in black individuals (0.01 annual age adjusted incidence per 100,000) (1616). Merkel cell carcinoma is more common in men than in women with a ratio of 2.3:1. This tumour typically occurs on the sun-exposed skin of older adults with a median age at presentation of 69 years.

Etiology
Anatomic and geographic distribution of Merkel cell carcinoma imply sun exposure as a major risk factor. A relatively high incidence of this neoplasm in solid organ transplant recipients and in patients with human immunodeficiency virus infection point towards an etiologic role of chronic immunosuppression.

Localization
The majority of Merkel cell carcinomas arise on sun-exposed skin. The most frequently affected sites are the head and neck (50%) and extremities (40%) (843). The trunk and genitalia are involved in less than 10% of cases. Exceptional cases on mucosal surfaces have been recorded.

Clinical features
Most tumours are solitary and present as a painless dome shaped nodule or indurated plaque that is red, violaceous or skin-coloured and, at times, ulcerated. Growth is typically rapid over a period of weeks to months. Most lesions measure less than 2 cm in diameter.

Tumour spread and staging
Merkel cell carcinoma has a high incidence of local recurrence, regional lymph node metastasis and, ultimately, haematogenous and/or distant lymphatic spread (517). Clinical staging after histopathologic diagnosis should include at the minimum a chest x-ray and CT of the chest and abdomen to exclude other possible primary sites and to evaluate for the presence of metastatic disease. Merkel cell carcinoma in locations other

Fig. 6.9 Merkel cell carcinoma. A Rapidly growing, violaceous nodule on the forehead (courtesy Dr. Scott Dinehart). B Pagetoid involvement of the epidermis. C Trabecular growth is one of the architectural patterns of Merkel cell carcinoma.

S. Kohler
H. Kerl
than the eyelid, vulva and penis is staged according to the TNM system for non-melanoma skin cancers.

**Histopathology**

Merkel cell carcinoma is a small blue cell neoplasm, composed of cells of uniform size with a round to oval nucleus and scant cytoplasm. Nuclear membranes are distinct, the chromatin is finely dispersed and nucleoli are usually inconspicuous. Mitotic figures and nuclear fragments are numerous. Focal spindle cell differentiation may be present. The tumour is centred on the dermis and frequently extends into the subcutaneous fat. The epidermis may be involved in a pagetoid fashion (1384) and in exceptional cases the tumour cells are entirely limited to the epidermis. Ulceration of the epidermis occurs in a subset of cases. This neoplasm forms diffuse sheets and solid nests in the dermis. A trabecular growth pattern, ribbons or festoons can be seen mainly in the periphery. Pseudorosette formation is rare. The dermis occasionally shows a desmoplastic response. Larger lesions may show zonal tumour necrosis and angiolymphatic involvement is commonly present around the primary neoplasm. Not infrequently, Merkel cell carcinoma occurs in intimate association with an in situ or invasive squamous cell carcinoma (2450). Biphenotypic differentiation with squamous or eccrine foci or even tripartite differentiation with squamoid, glandular and melanocytic foci are described. Areas of partial or complete regression can be found (529).

The histopathologic differential diagnosis includes basal cell carcinoma, melanoma, lymphoma, eccrine carcinoma, poorly differentiated squamous cell carcinoma, metastatic neuroblastoma, primary peripheral primitive neuroectodermal tumour and metastatic neuroendocrine carcinoma.

**Immunohistochemistry**

Merkel cell carcinoma shows epithelial and neuroendocrine differentiation. Tumour cells express low molecular weight cytokeratins (detectable by specific or broad spectrum cytokeratins such as AE1/AE3, CAM5.2, pan-cytokeratin), epithelial membrane antigen and the epithelial marker BER-EP4. Cyto-keratin 20 is a sensitive and quite specific marker for Merkel cell carcinoma (1604). The staining pattern for low molecular weight cytokeratins and CK20 typically is as paranuclear dots, but may also show cap-like paranuclear or diffuse cytoplasmic staining (1138). CK20 is useful in combination with thyroid-transcription factor-1 to differentiate between Merkel cell carcinoma (CK20 positive, TTF-1 negative) and small cell carcinoma of the lung (<10% CK20 positive, TTF-1 positive) (463). CK20 and broad spectrum cytokeratin are also useful for the detection of occult micrometastases in sentinel lymph nodes (2287). Markers of neuroendocrine differentiation include chromogranin, synaptophysin, neuron-specific enolase, bombesin, somatostatin, calcitonin, gastrin and others. Merkel cell carcinoma also expresses CD117, the KIT receptor tyrosine kinase (2284), and in approximately a third of cases CD99 (1707). The tumour cells are negative for leukocyte common antigen and S-100.

**Histogenesis**

The histogenesis of Merkel cell carcinoma is controversial. A direct histogenetic link between tumour cells and Merkel cells is unproven despite overlap in the morphologic, immunologic and ultrastructural features. Another theory postulates that Merkel cell carcinoma arises from a primitive epidermal stem cell with a capacity to differentiate towards neuroendocrine cells and keratinocytes.

**Somatic genetics**

A deletion on the short arm of chromosome 1 (1p36) is commonly observed and is shared with other neoplasms of neural crest derivation including neuroblastoma and melanoma (2208). Numerous other chromosomal abnormalities are described in Merkel cell carcinoma, the most common being trisomy 6, affecting nearly 50% of tumours. As of yet, no candidate oncogenes or tumour suppressor genes have been identified.

**Prognostic factors**

Diverse clinical prognostic factors include older age, location on head and neck, size greater than 2 cm, immunosuppression and advanced disease stage (517, 843, 2208). Adverse histopathologic and immunologic features include more than 10 mitotic figures per single high power field, small cell size, angiolymphatic invasion, and immunoreactivity for CD44 (1803).
Granular cell tumour

Definition
Granular cell tumours (GCT) encompass a cytologically similar, but etiologically and clinically diverse group of entities that are characterized by proliferation of large cells with granular-appearing eosinophilic cytoplasm. Herein, only the variant with direct or indirect evidence of peripheral nerve sheath association and common cutaneous manifestation is considered.

ICD-O code 9580/0

Synonyms
Granular cell Schwannoma, granular cell nerve sheath tumour, granular cell myoblastoma, Abrikossoff tumour

Historical annotation
The tumour was thought to be derived from skeletal muscle cells by Abrikossoff (1927). The association with nerve sheath differentiation was proposed by Feyrter (1935).

Epidemiology
GCT affects mainly adults (age 30-50), but can occur at any age. The male to female ratio is about 1:3; it is more common in African Americans than in Whites (78,245,1354). The tumour is characteristically solitary, and about 70% are located in the head and neck area, including 30% of these in the tongue. Other common locations are the breast and the proximal extremities. GCT usually involves the skin and subcutis; however, visceral involvement can also occur, primarily in the respiratory tract (larynx and trachea) and the gastrointestinal tract (oesophagus, large bowel, and anal area) (245). In about 10% of the cases GCT is multifocal, simultaneously involv-

Fig. 6.11 Granular cell tumour. A Reactive squamous pseudoepitheliomatous hyperplasia with prominent cytologic atypia mimicking squamous cell carcinoma. The granular cells are intermingled with squamous epithelial cells. B Granular cell tumour. The brightly eosinophilic granular cells form solid nests and strands infiltrating the dermis. C Granular cell tumour associated with a peripheral nerve. The granular cells have polygonal shape, distinct cytoplasm and eosinophilic granular cytoplasm with round, fairly uniform nuclei. D The large, ovoid, brightly eosinophilic globules surrounded by clear halo represent giant lysosomes.
ing the skin, submucosa, and viscera (577). Congenital presentation has also been reported. No definite association with neurofibromatosis type 1 has been established (1642,2577).

**Clinical features**

GCT usually presents as an asymptomatic or occasionally tender or pruritic, skin-coloured or brown-red, firm dermal or subcutaneous papulo-nodule, ranging in size from 0.5-3.0 cm in diameter. Verrucous changes of the surface epithelium are common, whereas ulceration is uncommon. The cutaneous tumours grow slowly; most symptoms are related to visceral locations.

**Macroscopy**

GCTs are nodular, but not encapsulated, and present as firm dermal or subcutaneous masses with a thickened or verrucous epidermal surface. On cut-surface the tumour has a pink-yellow, finely granular appearance (2084,2490).

**Histopathology**

The tumour forms poorly cohesive nests, strands, fascicles, and sheets of polygonal, pale eosinophilic cells in the dermis and subcutis. Commonly, the cells form indistinct delicate fascicles that infiltrate the dermal collagen and extend to the subcutaneous septa. A variant of GCT with a distinctly plexiform growth pattern has been documented (1392). Perineural spread is a common feature. The cells have an abundant granular, faintly eosinophilic cytoplasm with round, small, hyperchromatic nuclei. The fine, eosinophilic, intracytoplasmic granules correspond to lysosomes, which are PAS positive and diastase resistant. Occasional larger, brightly eosinophilic ovoid bodies surrounded by a clear halo can be identified within the granules representing residual “giant” lysosomes. Interspersed between the granular cells, there are spindle cells with fibroblast-like features and histiocyte-like cells often with triangular, coarsely granular eosinophilic lysosomes designated as “angular bodies”. Nuclear pleomorphism, prominent nucleoli, and mitotic figures are uncommon. A characteristic feature of most cutaneous GCTs is the overlying pseudoepitheliomatous hyperplasia, which can be so extensive that it can mimic a verruca or a well-differentiated squamous cell carcinoma.

**Immunohistochemistry**

GCT expresses markers associated with both neural (S-100 protein, PGP 9.5, neuron specific enolase, laminin, NGFR, calretinin, peripheral myelin proteins, P2-P0, myelin basic protein, CD57) and histiocytic (CD68, a-1-antitrypsin) differentiation. The tumour cells are positive for vimentin. Most studies report a negative reaction for neural filaments and GFAP (246,743,1063,1487,1540,1714).

**Variants**

**Granular cell epulis of infancy**

This is a rare, polypoid tumour of the alveolar ridge of the gingiva of the newborn with a predilection for girls. The tumour has cytologic features similar to GCT, but lacks globular cytoplasmic inclusions, argentate body histiocytes, and contains a distinct plexiform capillary pattern. The immunohistochemical profile is also different; the lesions are negative for S-100 protein, NSE, laminin, MBP, CD57, and α-1-ACT (740,1367,1764,2528).

**Malignant granular cell tumour**

These are extremely rare and comprise less than 2% of all granular cell tumours. The age and sex distribution is similar to that of their benign counterparts, but they are more common on the extremities (particularly on the thighs) rather than the head and neck areas, or the oral mucosa. Malignant GCTs grow rapidly, often ulcerate, invade locally and tend to spread via extensive metastases. Histologically and cytologically two forms can be distinguished: the more common type of malignant GCT is essentially identical to the benign tumour. Since cytologic atypia or mitotic activity are not reliable biologic indicators, correlation of clinical data (large size, rapid growth, ulceration) with the histologic features (necrosis, spindling, and lymphocapillary invasion) should guide in the diagnosis of malignancy. Additional features cited as useful for predicting malignancy are vesicular nuclei with large nucleoli and a mitotic rate greater than 2 mitoses/10 HPF. The second type of malignant GCT is quite rare; both the primary tumour and its metastases display histologic and cytologic characteristics of malignancy. The immunophenotype of malignant GCT is also similar to that of the benign tumour, however the proliferation markers (Ki-67) show increased labelling indices, and p53 expression is prominent (2084).

**Genetics**

Only limited genetic studies have been performed on malignant GCT of the soft tissue. This showed two clonal karyotypes. One atypical tumour was aneuploid and all 11 benign tumours were either diploid (9 cases) or hyperdiploid (2 cases) (627).

**Prognosis and predictive factors**

GCT is benign, however local recurrence is common due to incomplete removal complicated by the typical perineural spread. The malignant variants are aggressive tumours and usually have numerous local recurrences before distant spread. Their overall prognosis is poor, with metastases developing within two years in the majority of cases and there is close to 60% mortality within three years (2084,2490). Because of the potential for recurrence and the morphologic overlap between benign and malignant GCT, complete excision is recommended.