CHAPTER 5

Soft Tissue Tumours

Most soft tissue tumours are benign, outnumbering malignant ones by about 100 to 1. Soft tissue sarcomas comprise over 50 histological types, many of which have more than one subtype. Their behaviour varies from indolent to very aggressive, with consequent variation in survival, according to histological type, grade, and sometimes genetic constitution, but the overall 5 year survival is about 65-75%. In general, sarcomas in skin or subcutis have a more favourable outcome than those located beneath deep fascia. Only those tumours with a predilection for the skin, and not already covered in the WHO Classification of Tumours of Soft Tissue and Bone are described in this chapter.
### WHO histological classification of soft tissue tumours

#### Vascular tumour
- Haemangioma of infancy: 9131/0
- Cherry haemangioma: 9120/0
- Sinusoidal haemangioma: 9120/0
- Hobnail haemangioma: 9120/0
- Glomeruloid haemangioma: 9120/0
- Microvenular haemangioma: 9120/0
- Angiolympoid hyperplasia with eosinophilia: 9120/0
- Spindle cell haemangioma: 9136/0
- Tufted angioma: 9161/0
- Arteriovenous haemangioma: 9123/0
- Cutaneous angiosarcoma: 9120/3

#### Lymphatic tumours
- Lymphangiomia circumscriptum: 9170/0
- Progressive lymphangioma: 9170/0

#### Smooth and skeletal muscle tumours
- Pilar leiomyoma: 8890/0
- Cutaneous leiomyosarcoma: 8890/3

#### Fibrous, fibrohistiocytic and histiocytic tumours
- Dermatomyofibroma: 8824/0
- Infantile myofibromatosis: 8824/1
- Sclerotic fibroma: 8823/0
- Pleomorphic fibroma: 8832/0
- Giant cell fibroblastoma: 8834/1
- Dermatofibrosarcoma protuberans: 8832/3
- Dermatofibroma (fibrous histiocytoma): 8832/0

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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (786) and the Systematized Nomenclature of Medicine [http://snomed.org](http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

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### TNM classification of soft tissue sarcomas

#### Primary Tumour (T)

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<td>T1a: superficial tumour*</td>
<td>T1b: deep tumour</td>
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### G Histopathological Grading

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### Stage grouping

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#### Notes:
- Regional node involvement is rare and cases in which nodal status is not assessed either clinically or pathologically could be considered NO instead of NX or pNX.

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From references [92,2219].

Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are classified as deep tumours.
Soft tissue tumours: Introduction

C. Fisher

Epidemiology
Age-standardized incidence rates of soft tissue sarcomas, which are fairly constant in most areas covered by cancer registration, range from 1-3 per hundred thousand population (1781). Sarcomas of cutaneous origin are relatively rare, and are far outnumbered by carcinomas, melanoma and benign mesenchymal neoplasms of skin and subcutis (superficial soft tissue). The most common benign tumours are lipomas, fibrous histiocytomas, vascular or smooth muscle lesions including angioleiomyomas, and nerve sheath tumours (schwannoma, neurofibroma). Some of these tumours are covered elsewhere (756). The vast majority are located superficially and do not exceed 5 cm in diameter. Sarcomas are mostly found in older adults. They arise mainly in the extremities, especially the thigh, followed by trunk, head and neck and retroperitoneum.

Etiology
Most soft tissue sarcomas arise spontaneously and are of unknown etiology. A small number arise in rare familial cancer syndromes with germline mutations. A number of other congenital and inherited syndromes are associated with benign and malignant soft tissue tumours; type examples include Mafucci syndrome (chondroid and vascular tumours) and Cowden disease (lipomas, haemangiomas). Further details can be found in the WHO Classification of Tumours of Soft Tissue and Bone (756). Non-hereditary genetic factors are also presumed to be pathogenetic in various tumour types which have consistent chromosomal translocations, although it is not known how or in what cell these rearrangements arise. Viruses associated with sarcomas include human herpes virus 8 (HHV8) in Kaposi sarcoma (434,2487), and EBV in some smooth muscle tumours in children and adults with immunosuppression, including transplant recipients and patients with HIV infection (1390,1547). Angiosarcoma complicating longstanding lymphoedema, especially after radical mastectomy (Stewart-Treves) might also be due to local immunosuppression (1995).

An association between exposure to herbicides, including dioxin, and sarcoma-genesis is controversial and remains unproven. Sarcomas can arise in the field of prior therapeutic irradiation. This is a dose- and time-related phenomenon, resulting mostly in subfascial, high-grade pleomorphic sarcomas after an interval of 5 or more years. Following irradiation for carcinoma of breast, low-grade cutaneous angiosarcomas have been described after an interval as short as 18 months (1772).

Clinical features
Benign and malignant tumours present as usually painless masses, with varying growth rate. Cutaneous lesions form a plaque or elevated nodule that can ulcerate when malignant. Large (>5 cm) superficial lesions, and all subfascial or deep-seated tumours, should be referred to a specialist multidisciplinary centre before surgery and preferably before biopsy (180).

Pathology
In general, malignant soft tissue neoplasms are characterized by nuclear pleomorphism, mitotic activity including abnormal forms, necrosis and vascular invasion. Some benign tumours, however, can show one or more of these features. Examples include nuclear atypia in cutaneous pleomorphic fibroma and atypical benign fibrous histiocytoma (which can also display necrosis), and frequent mitoses in nodular fasciitis. Detailed diagnostic criteria are provided for each subtype.

Diagnostic procedures
Investigation includes clinical assessment of size and depth of tumour, the use of imaging modalities, and biopsy.

Imaging
Imaging is of value for assessing the extent of a primary tumour and its relationship to normal structures, and for revealing metastases. Both computerized tomography (CT) and magnetic resonance imaging (MRI) are used. CT is particularly useful for tumours in body cavities, and for detecting pulmonary metastases. MRI can demonstrate intratumoural heterogeneity, including presence of solid, fatty, fibrous, haemorrhagic or necrotic tissue, and the interface between neoplastic and normal tissue including involvement of neurovascular bundles.

Biopsy
Superficial lesions smaller than 2-5 cm in diameter can be excised in their entirety. Larger ones, and all subfascial and deep-seated tumours need diagnostic sampling. For this, some practitioners prefer open incisional biopsy with an appropriately placed incision that is subsequently excised in continuity with the formal resection. Needle core biopsy, preferably using a Trucut or larger needle can provide diagnostic information for malignancy, subtype and grade, with high sensitivity and specificity in experienced hands (1021,1040). Fine-needle aspiration cytology is used in a few centres where a large volume of cases allows accrual of sufficient experience (46); it is not particularly sensitive for diagnosing malignancy in differentiated adipose or in sub-typing low-grade myxoid lesions, partly because the sample might not be representative.

Tumour spread and staging
The recent WHO classification of Tumours of Soft Tissue and Bone (756) recognizes three behavioural categories:
1. Benign tumours. These rarely recur locally, and those that recur do so in a non-destructive fashion and are usually cured by local excision. Exceptionally rarely, an otherwise (and histologically typical) benign tumour, such as cutaneous fibrous histiocytoma, can metastasize.
2. Intermediate tumours are those that...
are locally aggressive and/or very occasionally metastasizing. Locally aggressive tumours, such as fibromatosis, recur locally and infiltrate surrounding tissues. Rarely-metastasizing tumours are generally dermal or subcutaneous tumours which have a low (1-2%) but definite risk of metastasis, most often to regional lymph nodes but occasionally to lung. Examples are recorded for plexiform fibrohistiocytic tumour (2028) and angiomatoid fibrous histiocytoma (693).

3. Malignant tumours infiltrate and recur locally and have an appreciable risk of metastasis (exceeding 20%).

Grading
This is an attempt to predict clinical behaviour based on histological variables. Grading of a tumour should be done on material from a primary untreated neoplasm, though change (increase) of grade can be noted in recurrent or metastatic tumour. It is not applicable to all sarcomas; for example, angiosarcoma, clear cell sarcoma and epithelioid sarcoma are always considered to be of high-grade malignancy. Several grading systems have been proposed, but that of the French Cancer Centres is gaining wide usage (917). Briefly, tumours are given a score of 1, 2 or 3 depending on degree of differentiation; 1, 2 or 3 for number of mitoses per 10 hpf (<10, 11-20, or >20); and 0-2 for amount of necrosis (0, <50%, >50%). A total score count of 2 or 3 is classified as grade 1, a score count of 4 or 5 as 2, and a score of 6, 7 or 8 as grade 3.

Staging
A widely used staging system for soft tissue sarcomas is that of the International Union against Cancer (UICC) (TNM system) and American Joint Commission on Cancer (AJCC) (892,2219). Unlike for many other tumours, staging of sarcomas includes histological grading as well as tumour size and depth from surface, regional lymph node involvement and distant metastasis.

Prognosis and predictive factors
Completeness of excision (assessed by clear surgical margins in the excision specimen) is the most important factor in prevention of local recurrence (2376). Some sarcomas, notably epithelioid sarcoma, are relentlessly recurrent, even though they might not metastasize until late in the course of the disease (2238). For metastasis, general adverse factors are large tumour size and increasing depth from surface. Thus, cutaneous sarcomas have a lower risk of metastasis than those located more deeply (2001); indeed, histologically malignant leiomyosarcomas confined to skin are essentially non-metastasizing tumours (1164). In some instances, histological subtype is predictive, but one of the principal factors in assessing prognosis and determining management is the histological grade. Low-grade sarcomas, however, when located in sites where complete surgical excision is difficult, such as retroperitoneum or head and neck, have a worse outcome than similar tumours in the extremities. Molecular genetic findings, especially fusion gene types, might relate to prognosis.
Haemangioma of infancy

Definition
Haemangioma of infancy (HOI) is a proliferation of benign capillaries characterized by perinatal or congenital onset, rapid proliferation in the first year, followed by spontaneous regression. Strong expression of GLUT1 is distinctive.

ICD-O code 9131/0

Synonyms
Infantile haemangioma, juvenile haemangioma.

Epidemiology
HOI is the most common tumour of infancy, affecting up to 10-12% of children (1051,1119). There is a predilection for females (at least 3:1) (1663), Caucasians and premature infants (1051,1853). Presentation is exclusively in infants, although involuting lesions persist into childhood.

Etiology
The unique immunophenotypic resemblance of HOI and placental vessels suggests shared regulatory mechanisms, or possibly a common cellular origin (1723). Two recent studies have demonstrated endothelial cell clonality in HOI (295,2452), suggesting a possible role for somatic mutation (2452).

Localization
It most commonly affects the skin and subcutis of the head and neck, followed by the trunk and extremities. Visceral involvement, although rare, is most common in the liver, followed by the lung, brain, and intestine (746).

Clinical features
Nascent lesions appear as blanched macules or erythematous patches, often with central telangiectasias, typically around 2 weeks of age. Approximately 30% are congenital. Following a rapid growth phase of 3-18 months, involution occurs over several years, often leaving a fibrofatty residuum. Most develop as focal masses, although some show a diffuse, segmentally distributed pattern (2453). Although usually solitary, many affected infants have several lesions. Rare cases of “diffuse neonatal haemangiomatosis” have multiple small skin lesions accompanied by visceral lesions (1454). Large facial haemangiomas may be associated with posterior fossa malformations, aortic coarctation, cardiac defects, arterial abnormalities, eye abnormalities, and sphenoidal clefing (PHACES syndrome) (1591). Lumbo-sacral haemangiomas may be associated with spinal dysraphism, tethered cord syndrome, and other caudal abnormalities (850). MRI in the proliferative phase shows a tumoral mass with flow voids.

Macroscopy
Proliferative phase lesions show solid tan lobules, are well-defined but not encapsulated.

Histopathology
Proliferative phase lesions are cellular masses of plump endothelial cells and pericytes with abundant cytoplasm and enlarged nuclei that together form capillaries with tiny rounded lumina. Investing basement membranes are multilaminated; mast cells are numerous. The capillaries are arranged in delicately defined lobules, separated by thin fibrous septa or normal intervening tissue. Mitotic figures may be numerous; supportive arteries and veins are prominent. During involution, endothelial cells and pericytes flatten, lumina enlarge, and mitotic figures diminish. Capillaries progressively drop out and are replaced by loose connective tissue. End-stage lesions often show isolated groups of “ghost” vessels composed of thick, acellular basement membrane rings containing apoptotic debris.

Immunohistochemistry
All stages are distinguished from other vascular tumours by their strong endothelial positivity for several antigens, including GLUT1, Lewis Y antigen, FcγRII, and IGF-II (1722,1723,1942). Basement membranes strongly express merosin (1723).

Differential diagnosis
Proliferative phase HOI must be distinguished from other cellular vascular proliferations including congenital non-progressive haemangioma, kaposiform haemangioendothelioma, tufted angioma, pyogenic granuloma, and intramuscular haemangioma. Involuting HOI may mimic vascular malformations. The characteristic GLUT1 immunoreactivity of HOI is helpful in routinely fixed specimens (1722).

Somatic genetics
HOI are generally sporadic, although autosomal dominant inheritance has been suggested in several kindreds (259). Monozygotic and dizygotic twins show no significant difference in concordance for haemangioma development (464). No cytogenetic abnormalities have been reported.

Cherry haemangioma

Definition
Cherry haemangioma (CH) is a benign, acquired, well-circumscribed aggregate of dilated capillaries and venules in the superficial dermis.

ICD-O code 9120/0

Synonyms
Campbell de Morgan spots, de Morgan spots, senile haemangioma.

Epidemiology
CH is rare before puberty, with a few lesions developing in early adulthood. Number and incidence increase through adulthood, becoming almost universally present with large numbers in some patients. Sex predilection is not a feature, with the exception of lesions that can occur in pregnancy (169).
**Etiology**
Age is the most common factor in the development of the majority of lesions. Eruptive cases have been reported after exposure to sulphur, mustard gas, bromide compounds and 2-butoxyethanol solvent (510,747,1901). There are two reports of outbreaks in populations, without definite causes (1058,2145). CH lesions that develop in pregnancy can involute in the puerperium and eruptive lesions have been reported in two patients with elevated prolactin levels suggesting a hormonal factor in some lesions (169,1924).

**Localization**
The majority of lesions are located on the trunk and upper limbs with relative sparing of the head and neck. There is no predilection for exposed skin.

**Clinical features**
CH begins as a barely discernible red macule that enlarges to become a slightly elevated erythematous papule 1-5 mm in diameter. It may resist blanching with pressure.

**Histopathology**
CH is a tightly grouped, well-circumscribed collection of capillary vessels and venules in the superficial dermis with minimal dilatation of some lumena. Elevated lesions show epidermal atrophy with loss of rete ridges and sometimes an epithelial collarette.

**Histogenesis**
Ultrastructural three-dimensional studies show that CH is composed of interconnected spherical and tubular dilatations of venous capillaries and postcapillary venules in the dermal papillae (303).

**Somatic genetics**
A genetic or angiogenic factor has not yet been implicated in the development of CH.

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**Sinusoidal haemangioma**

**Definition**
Sinusoidal haemangioma is a benign vascular neoplasm in which cavernous appearing vascular spaces occur in a well circumscribed, generally small papule or nodule. Most clinicians use the term cavernous haemangioma to refer to much larger and more poorly circumscribed lesions in infants.

**ICD-O code** 9120/0

**Synonym**
Cavernous haemangioma (erroneous, in part).

**Epidemiology**
Most reported cases are in adult women.

**Localization**
The arms and torso are the most common sites (366).

**Clinical features**
Most sinusoidal haemangiomas are freely movable deep dermal or subcutaneous papules or small nodules. When deep, they may be colourless or bluish, but when superficial, they may be red.

**Histopathology**
Sinusoidal haemangiomas are round or oval and very well circumscribed dermal or subcutaneous neoplasms (366,1680). They are composed of thin walled vessels with capacious round lumena. The vessels are very closely apposed to one another ("back to back appearance"). Occasional lesions have smooth muscle in their walls. Thrombosis of vascular channels occurs in a proportion of cases. This can lead to intravascular papillary endothelial hyperplasia (a potential stimulant of angiosarcoma in a partial biopsy) and calcification may result (1680).

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**Hobnail haemangioma**

**Definition**
Hobnail haemangioma (HH) (389,916, 1584,1896,2052) is a benign vascular proliferation characterized by a wedge-shaped dermal proliferation of irregular vascular channels lined in its superficial portion by endothelial cells with hobnail morphology.

**ICD-O code** 9120/0

**Synonym**
Targetoid haemosiderotic haemangioma

**Epidemiology**
HH is relatively rare and presents mainly in young to middle-aged adults with predilection for males.

**Etiology**
Trauma may play a role in the formation...
of these lesions (2052). One possible origin is via trauma to lymphangiomas or angiokeratomas, resulting in dispersion of endothelial cells and erythrocytes into the surrounding dermis.

**Localization**
Most cases occur on the lower limbs with predilection for the thigh followed by the upper extremities and the trunk. Rare lesions have been reported in the oral cavity including the tongue and gingivae.

**Clinical features**
Some lesions show a characteristic targetoid clinical appearance with variably pigmented ecchymotic haloes secondary to bleeding and haemosiderin deposition within the tumour (2052). Most often however, the clinical presentation is non-distinctive and the clinical differential diagnosis includes haemangioma, naevus or fibrous histiocytoma. HH is asymptomatic, usually less than 2 cm in diameter and increases in size very slowly. Patients usually describe cyclic changes (389). Multiple lesions are exceptional. Similar histological changes may occur after trauma (481).

**Histopathology**
The most striking low-power feature is the presence of a wedge-shaped vascular proliferation consisting of superficial, dilated and thin-walled vascular channels lined by bland endothelial cells that appear flat or have hobnail morphology. Some of the vascular channels resemble lymphatics. Focally, intraluminal small papillary projections with collagenous cores are occasionally seen. As the vascular channels descend further into the reticular dermis they gradually become smaller and disappear. Inflammation is not usually a feature. Haemorrhage and haemosiderin deposition are prominent but vary according to the stage of evolution. A Perls stain may be useful in highlighting the haemosiderin.

**Immunohistochemistry**
The endothelial cells in HH stain diffusely for vascular markers including CD31 and VWF (von Willebrand factor). CD34 is usually negative or very focal. A layer of alpha-smooth muscle actin pericytes surrounds some of the vascular channels. The positive staining for vascular endothelial growth factor receptor-3 (VEGFR-3) in some cases has led to the suggestion that HH displays lymphatic differentiation (1584). VEGFR-3 is however, not entirely specific for lymphatic endothelium. Staining for human herpes virus 8 is consistently negative (932).

**Differential diagnosis**
Kaposi sarcoma differs by the absence of dilated blood vessels lined by hobnail cells.

**Prognosis**
The lesion is entirely benign and there is no tendency for local recurrence.

**Glomeruloid haemangioma**

**Definition**
Glomeruloid haemangioma is a benign vascular proliferation that occurs inside ectatic blood vessels, producing a pattern reminiscent of renal glomeruli.

**ICD-O code**
9120/0

**Epidemiology**
This is a very rare vascular proliferation that occurs exclusively in patients with POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal paraproteinaemia and Skin lesions), which is associated with multicentric Castleman disease (440,2562). Multiple haemangiomas occur in 24-44% of all patients with POEMS syndrome, with most being cherry-type haemangiomas (1301,2312,2580). The reported cases of glomeruloid haemangiomas show female predominance, with patients ranging in age from 40-68 years (440,1278,1285,1965,2083,2380,2562).
Etiology
Glomeruloid haemangioma has so far only been found in patients with POEMS syndrome. Its development may be mediated by circulating vascular endothelial factor, which is present at high titres in the blood of most patients with POEMS syndrome (2225, 2464).

Localization
The lesions are mainly found on the trunk, face and proximal limb, and exceptionally also in the fingers and deep soft tissues (440, 1278, 1285, 1965, 2380, 2562).

Clinical features
The lesions manifest as multiple purplish-red papules or nodules, ranging in size from a few to 15 mm (1278, 1285, 1965, 2380, 2562). They occur in patients already known to have POEMS syndrome, or as an early phenomenon before the full-blown syndrome develops (1278, 1285, 1965, 2083, 2380, 2562).

Histopathology
Glomeruloid haemangioma is mainly centred in the upper and mid dermis. It is characterized by tufts of proliferated, coiled capillaries projecting inside thin-walled ectatic blood vessels, mimicking renal glomeruli. The “sinusoidal” endothelial cells that line the ectatic vascular spaces and the surface of the tufts have dark-staining nuclei (“sinusoidal endothelium”), while those that line the capillaries have plumper and paler nuclei. “Interstitial” cells containing eosinophilic hyaline globules are also seen.

Immunohistochemistry
On immunohistochemical staining, the endothelial cells of the capillary loops stain for CD31 and CD34, and they are well supported by actin-positive pericytes. The sinusoidal endothelial cells covering the tufts are positive for CD31 but not CD34, while those lining the ectatic vascular spaces are strongly CD31 positive but weakly CD34 positive. The eosinophilic globules probably represent immunoglobulin. The cells that contain these globules represent a mixture of histiocytes (CD68+) and endothelial cells (CD31+).

Precursor lesions
Progression from cellular immature, non-specific, vascular proliferation with slit-like canals reminiscent of tufted angioma to classical glomeruloid haemangioma has been reported (2562). In addition, cherry-type haemangiomas with minia
ture glomeruloid structures formation can coexist with glomeruloid haemangiomas in patients with POEMS syndrome (440). Thus these might represent precursor lesions of glomeruloid haemangioma.

Histogenesis
The currently favoured view is that glomeruloid haemangioma is a reactive vascular proliferation, perhaps representing a distinctive form of reactive angioendotheliomatosis.

Prognosis and predictive factors
Glomeruloid haemangioma per se is a totally innocuous lesion. The outcome of the patients depends on the underlying POEMS syndrome.

Microvenular haemangioma
Definition
Microvenular haemangioma is an acquired, slowly growing asymptomatic lesion with an angiomatous appearance (1080).

ICD-O code 9120/0

Etiology
A histogenetic relationship between microvenular haemangioma and hormonal factors such as pregnancy and hormonal contraceptives has been postulated (144, 2065), but this feature has not been corroborated by other authors. An example of microvenular haemangioma has developed in a patient with Wiskott-Aldrich syndrome (1939). Haemangiomas identical to microvenular haemangioma can be seen in patients with POEMS syndrome (25).

Localization
It most commonly affects the upper limbs, particularly the forearms.
However, lesions on the trunk, face and lower limbs have also been recorded (65,1061).

**Clinical features**
Microvenular haemangiomas appear as sharply circumscribed, bright red, solitary lesions varying in size from 0.5-2 cm.

**Histopathology**
Microvenular haemangioma appears as a poorly circumscribed proliferation of irregularly branched, round to oval, thin-walled blood vessels lined by a single layer of endothelial cells. They involve the entire reticular dermis and a variable degree of dermal sclerosis is present in the stroma. The lumina of the neoplastic blood vessels are inconspicuous and often collapsed with only a few erythrocytes within them.

The main differential diagnosis is with Kaposi sarcoma in the patch stage. Kaposi sarcoma shows irregular anastomosing vascular spaces, newly formed ectatic vascular channels surrounding pre-existing normal blood vessels and adnexa (promontory sign), plasma cells, hyaline (eosinophilic) globules, and small interstitial fascicles of spindle cells. All of these features are absent in microvenular haemangioma.

**Immunohistochemistry**
Immunohistochemically, the cells lining the lumina show positivity for factor VIII-related antigen and Ulex europaeus I lectin (144,1080,2065) which qualifies them as endothelial cells. Some smooth muscle actin positive perithelial cells have been also described surrounding this vascular space (65,1061).

**Prognosis**
Microvenular haemangioma is a benign neoplasm and it is cured by simple excision.

**Angiolympoid hyperplasia with eosinophilia**

**Definition**
Angiolympoid hyperplasia with eosinophilia (ALHE) is a benign skin or subcutaneous tumour that is a circumscribed combined proliferation of immature blood vessels and chronic inflammatory infiltrate usually containing eosinophils. Endothelial cells have a distinctive epithelioid or histiocytoid appearance with ample eosinophilic cytoplasm.

**Synonyms**
Epithelioid haemangioma, cutaneous histiocytoid angioma, pseudo- or atypical pyogenic granuloma, inflammatory angiomatous nodule, intravenous atypical vascular proliferation, nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis (201,1154,1967,1968,2381).

**Epidemiology**
ALHE was originally described as a lesion commonly found in young women on the head and neck (1011). Recent reviews show a wide age range peaking at 20-50 years without female predominance (738,1753). There is no predilection for Asian populations.

**Etiology**
Reactive vascular proliferation and inflammation (2441) in a traumatized vascular structure is a postulated cause of some ALHE lesions. History of antecedent trauma, histologic evidence of...
adjacent vascular damage \(\{738,2400\}\) and pre-existing arteriovenous malformation \(\{1754\}\) are found in some cases. Although earlier reported, HHV-8 has not been consistently found in ALHE \(\{1130,1241\}\).

Localization
ALHE most commonly occurs on the head and neck with a predilection for the forehead, scalp and skin around the ear \(\{738,1011,1753\}\). Occurrence on distal extremities and digits is not uncommon \(\{97\}\). Multiple other reported sites include trunk, breast \(\{1676\}\), oral mucosa \(\{1512,1530,1776\}\), orbital tissues \(\{145,1513\}\), vulva \(\{37,2125\}\) and penis \(\{2240\}\).

Clinical features
ALHE lesions are small red or violaceous papules or plaques with an average size of 1 cm, measuring up to 10 cm. When symptomatic they can be pulsatile, painful and pruritic with scale crust \(\{1011,1753\}\). When multiple they are usually grouped or zosteriform \(\{647\}\) and may coalesce. In contrast to Kimura disease, lymphadenopathy, eosinophilia, asthma and proteinuria are uncommon and serum IgE is usually normal \(\{97,441\}\).

Histopathology
The lobulated, circumscribed dermal or subcutaneous proliferation has a combined vascular and inflammatory component. Sometimes an origin from a medium-sized vessel, usually a vein, is seen. There are arborizing small blood vessels that may surround a larger vascular structure. The vessel walls have smooth muscle cells or pericytes and contain mucin. The endothelial cells have distinct abundant eosinophilic (epithelioid) cytoplasm that can be vacuolated. They protrude into and can occlude vascular lumina or form solid sheets that may mimic angiosarcoma \(\{2582\}\). Their nuclei have open chromatin, often with a central nucleolus and may protrude into lumina with occasional mitoses. Multinucleate cells that are endothelial sprouts or histiocyte-like cells can be present \(\{2020\}\). The density of the inflammatory component between vessels is variable with a prominence of lymphocytes and eosinophils. Plasma cells, mast cells and lymphoid follicles with reactive germinal centres can be present. Older lesions typically become more fibrotic, less inflammatory and their vascular nature becomes less conspicuous.

Immunoprofile
The endothelial cells are positive for CD31, CD34, VWF (VIIIrAg) and are keratin negative. The proliferative index of the endothelial cells has been reported as 5% using Ki-67 with negative staining for Cyclin D1 and bcl-2. This may support a reactive rather than neoplastic endothelial proliferation \(\{97\}\). Lymphocytes are a mixture of T- and B-cells. There is no light chain restriction \(\{97,1753\}\). One series has shown T-cell clonality in ALHE that may define a subgroup of lesions with a higher incidence of recurrences \(\{1241\}\).

Differential diagnosis
Kimura disease is a distinct clinicopathological entity, characterized by a more prominent lymphoid proliferation and less prominent vascular component with almost complete absence of epithelioid endothelial cells.

Prognosis and predictive factors
The lesions tend to persist if not completely excised and only rarely will they spontaneously regress. Local recurrence can occur and may be related to persistence of an underlying arteriovenous fistula that is not completely excised \(\{97,1753,1754\}\).

Spindle cell haemangioma

Definition
Spindle cell haemangioma is a benign...
vascular tumour composed of an intimate admixture of cavernous blood vessels and Kaposi sarcoma-like spindle cell vascular zones.

ICD-O code 9136/0

Synonym Spindle cell haemangioendothelioma (1807,2488)

Epidemiology The tumour is uncommon, and mainly affects children and young adults. Those who present late in adulthood usually have long-standing tumours (270,1807). There is no sex predilection.

Etiology In a small proportion of cases, spindle cell haemangioma develops in the setting of multiple enchondromas (Maffucci syndrome), Klippel-Trenaunay syndrome, venous malformation, early onset varicose veins, or congenital lymphoedema (709,754,1807). The onset in young patients and frequent finding of abnormal vessels around the lesion suggest that an underlying vascular malformation may predispose to the development of spindle cell haemangioma (754).

Localization They occur on the distal extremities and less commonly on the proximal limb, trunk, head and neck (1807). Exceptionally, it has been reported in the spleen (709).

Clinical features The tumour usually presents as a superficial, slow-growing, painless, solitary purplish mass, or multiple nodules within an anatomical region (1807). Rare examples may be painful (1784). The lesion is a discrete red-brown nodule that ranges in size from a few mm to over 10 cm, but most are smaller than 2 cm.

Histopathology Spindle cell haemangiomas are mostly found in the dermis and subcutis, and occasionally in the deep soft tissues. The tumour is often well-circumscribed but non-encapsulated. It is characterized by intricate blending of cavernous and solid spindle cell zones. The cavernous blood vessels are empty or filled with blood, and may contain organizing thrombi or phleboliths. In the spindle cell regions, short fascicles of spindle cells are interspersed with ramifying narrow vascular spaces. The spindle cells possess uniform, elongated, dark nuclei and eosinophilic cytoplasm. There are scattered single or groups of vacuolated cells or epithelioid cells with lightly eosinophilic cytoplasm. In about half of the cases, residual vessel walls can be found in the periphery of the lesion, indicating that the lesion is partly or entirely intravascular (754,1807). Intravascular extension of the lesion can sometimes be seen around the main lesion.

Immunohistochemistry The cells that line the vascular spaces stain for VWF (VIIIrAg), CD31 and variably for CD34. The spindle cells are negative for the various endothelial markers including CD34, and may show patchy and variable staining for actin (754,796,1667).

Differential diagnosis Spindle cell haemangioma can be distinguished from Kaposi sarcoma by the following features: irregular-shaped, dilated and ramifying vascular spaces rather than short narrow vascular slits among the spindle cells, presence of vacuolated endothelial cells, frequent partial or complete localization within muscular blood vessels, absence of eosinophilic hyaline globules, lack of CD34 immunoreactivity in the spindle cells, and lack of association with HHV-8 (1034).

Histogenesis There are controversies on the nature of spindle cell haemangioma, with theories ranging from neoplastic, malformative to hamartomatous (754,1100,1807). The lesion itself comprises heterogeneous cellular populations, including endothelial cells, pericyte-like cells, fibroblasts, smooth muscle cells and primitive mesenchymal cells.

Somatic genetics There are no molecular data on spindle cell haemangioma; one studied case shows a normal karyotype (754). The lesions are diploid on flow cytometric analysis (796,1035).

Prognosis and predictive factors Recurrence after local excision occurs in 50-60% of cases, and often results from new lesions developing within the same anatomical region due to intravascular extension. However, there is no metastatic potential.

Tufted angioma

Definition Tufted angioma is an unusual, acquired, benign vascular neoplasm characterized by slow, indolent growth (1153,1475).

ICD-O code 9161/0

Synonyms Tufted haemangioma, progressive capillary haemangioma, angioblastoma of Nakagawa.

Epidemiology Tufted angioma most commonly affects children and young adults, but both congenital and very late onset cases have been described (995,1264).

Histopathology Another example of a tufted angioma present in the dermis and subcutaneous tissue.
Localisation
Tufted angioma favours the shoulders, upper chest, back, and neck (1747), although examples of these lesions have also been reported on the oral mucosa, extremities and head (1289, 2458).

Clinical features
The most common forms of presentation are enlarging erythematous, brown macules or plaques with an angiomatous appearance. In other instances the lesions resemble granulomas or a connective tissue naevus. Pain and hyperhidrosis have been described (216, 2291). Raised papules or nodules resembling pyogenic granulomas are sometimes seen within the lesion and occasionally they adopt a linear arrangement (1765). In some cases the patients present with sclerosing plaques (412). Tufted angiomas have been associated with vascular malformations including naevus flammeus (1267, 1601), pregnancy (1272), non-regressing lipodystrophy centrifugalis abdominalis (1032), and liver transplant (482). In some cases of Kasabach-Merritt syndrome the underlying lesion is a tufted angioma (691, 692, 2136). In most cases the growth is halted after some years, and in some cases there is a slight tendency towards spontaneous regression (1131). Tufted angioma grows slowly and insidiously, and may eventually come to cover large areas of the body.

Histopathology
There are multiple individual vascular lobules within the dermis and subcutaneous fat. These aggregations are more prominent in the middle and lower part of the dermis. Each lobule is composed of aggregates of endothelial cells that whorl concentrically around a pre-existing vascular plexus. Some lobules bulge into the walls of dilated thin-walled vascular structures, creating a slit-like or semi-lunar appearance of vessels. This peculiar shape in addition to the angiocentricity of the vascular structures prompted the name “tufted angioma.” Small capillary lumina are identified within the aggregations of endothelial cells. Unusual histopathologic findings in tufted angioma include a mucinous stroma, abundant sweat glands (137), an intravascular location (795) of the lesion and a proliferation of lymphatic-like channels.

Immunohistochemistry
Cells in the capillary tufts are weakly positive or negative for VWF (VIIIrAg). They exhibit strong positivity for CD31, CD34 and alpha-smooth muscle actin (1156, 1709). The cells that show reactivity for smooth muscle actin, most likely represent pericytes.

Electron microscopy
Ultrastructural studies have shown characteristic crystalloid inclusions within endothelial cells in addition to Weibel-Palade bodies (1709).

Genetics
Most cases are sporadic, although a family with several members affected by tufted angioma has been reported (993). In this particular family the mode of transmission was autosomal dominant.

Prognosis
Tufted angioma showing spontaneous regression is a rare event. Although benign, symptomatic lesions need to be treated (1131, 1709, 1948).

Bacillary angiomatosis

Definition
Bacillary angiomatosis is a reactive vascular proliferation caused by infection with bacteria of the genus Bartonella, most commonly B. henselae and B. quintana (507, 855, 1383, 1845, 2492).

Synonyms
Disseminated pyogenic granulomas (not generally accepted), epithelioid angiomatosis.

Epidemiology
Bacillary angiomatosis most commonly occurs in immunosuppressed patients although there have been a few reports in apparently immunocompetent patients, both adults and children (504, 507, 1233, 1383, 1793, 1845, 2111, 2206, 2325). Bacillary angiomatosis has most frequently been seen in HIV/AIDS patients.

Localisation
Cutaneous involvement may occur at any site and less commonly lesions may involve mucosal surfaces and deeper soft tissue such as muscle, bone, lymph node and liver (peliosis hepatis) (442, 507, 1383, 1845, 2085).

Clinical features
The lesions present as multiple reddish to red-brown cutaneous nodules and occasionally as subcutaneous nodules. In immunocompetent patients there may be fewer nodules (507, 1383, 1845).

Histopathology
Sections show a lobular proliferation of well-formed vessels with plump occasionally epithelioid endothelial cells. There is an oedematous to fibrous stroma with a variable infiltrate of neutrophils with nuclear dust, macrophages and ill-defined pale basophilic granular material (representing the bacteria). Diagnosis is made by identifying the characteristic coccobacillary organisms with a Warthin-Starry or Giemsa stain (507, 1383, 1845).

Differential diagnosis
Pyogenic granuloma lacks the characteristic basophilic granular material and the dispersed pattern of neutrophils seen in bacillary angiomatosis. Histologically identical lesions can be seen in verruca peruana (verruga peruana).
**Prognosis and predictive factors**
The infection may be cleared by antibiotics with resolution of the lesions. The overall prognosis depends upon the immune status of the patient and sites of involvement (507,1383,1845).  

**Reactive angioendotheliomatosis**

**Definition**
Reactive angioendotheliomatosis (RA) is a relatively rare condition associated with diverse systemic diseases, usually confined to the skin and characterized by a multifocal dermal proliferation of capillaries (1559,2513).

**Synonym**
Diffuse dermal angiomatosis. The so-called malignant angioendotheliomatosis represents a form of intravascular lymphoma not related to reactive angioendotheliomatosis (2512).

**Epidemiology**
Presentation is mainly in adults with no sex predilection. Occurrence in children is exceptional (304).

**Localization**
There is a predilection for the trunk and limbs.

**Clinical features**
Clinical presentation is variable and consists of fairly widespread erythematous macules, papules, nodules and plaques (1559,2513). Purpura is a frequent finding. Ulceration is very rare. Many systemic illnesses are related to the development of RA and it can be said that this condition often represents a marker of systemic disease. Patients affected with RA not uncommonly are immunosuppressed as a result of transplantation. Many conditions have been associated with reactive angioendotheliomatosis including valvular cardiac disease, alcoholic cirrhosis, rheumatoid arthritis, polymyalgia rheumatica, cryoglobulinaemia, the antiphospholipid syndrome, and sarcoidosis (551,1385,1559,2178,2341,2361). A more localized variant may be seen in some patients and it is usually associated with peripheral vascular atherosclerosis or iatrogenic arteriovenous fistulas (1266,1276,1918).

**Histopathology**
Histologically, the dermis and rarely the superficial subcutaneous tissue show numerous clusters of closely packed capillaries. Many of these capillaries proliferate within pre-existing blood vessels. Cytological atypia is mild or absent but endothelial cells are often prominent and may show focal epithelioid cell change. A layer of pericytes surrounds the newly formed small vascular channels. Extravasation of red blood cells tends to be prominent. PAS positive microthrombi are numerous in cases associated with cryoglobulinaemia. Dermal changes resembling fasciitis have also been described.

**Differential diagnosis**
Distinction from Kaposi sarcoma is easy as in RA there is no proliferation of individual irregular lymphatic-like channels around pre-existing normal blood vessels, proliferating vascular channels are surrounded by a layer of pericytes and inflammatory cells are very rare or absent. Tufted angioma may be distinguished from RA by the typical cannonball appearance at scanning magnification and the presence of slit-like crescent shaped lymphatics around individual tufts in the former. An unusual entity characterized by the presence of aggregates of histiocytes within vascular lumina and described as intravascular histiocytosis has been recently described and may closely mimic reactive angioendotheliomatosis (1935). Distinction from the latter may be difficult and in difficult cases immunohistochemistry is useful in demonstrating the histiocytic nature of the intravascular cells.

**Prognosis and predictive factors**
RA tends to be self-limiting in the majority of cases with complete spontaneous resolution over weeks or months.

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**Fig. 5.10 Bacillary angiomatosis.**  
A Low power view of a skin lesion of bacillary angiomatosis shows dome shaped expansion of the upper dermis due to a proliferation of small well formed vessels.  
B High power view showing the plump endothelial cells lining the vessels.  
C A Warthin-Starry stain shows the small cocco-bacillary organisms.
Verrucous haemangioma

Definition
Verrucous haemangioma (VH) is an uncommon variant of haemangioma with capillary or cavernous features (444, 2489). It is evident at birth or in early childhood and enlarges and becomes hyperkeratotic in later life.

Synonyms
Haemangioma unilateralis naeviforme, unilateral verrucous haemangioma, angiookeratoma circumscriptum naeviforme, naevus vascularis unius lateralis, keratotic haemangioma, naevus angiokeratoticus, naevus keratoangiomaticosus (363).

Epidemiology
VH is usually apparent at birth or in the first few years of life (1102). The condition is rare, and there is no known gender predilection.

Localization
VH is almost always a unilateral isolated condition, with most cases affecting the leg. Less commonly, it presents on the arm. It is not common on the trunk, but when present on the back in association with underlying spinal malformation, it is a component of Cobb syndrome.

Clinical features
The condition usually presents with lesions that are clustered, discrete to nearly confluent, bluish-red, well demarcated, soft and compressible (363, 444, 1102). The lesions that comprise these clusters may coalesce to form large lesions that cover broad areas over time. Satellite lesions are typical. The condition may show linear or serpiginous distribution. Lesions become hyperkeratotic over time and show a brown to bluish-black appearance. Hyperkeratosis may be so pronounced as to appear verrucous; consequently, the lesion may be mistaken clinically for a wart or keratosis (2560). Size usually allows distinction from the later two, as verrucous haemangioma tends to be large.

Histopathology
Within the superficial and deep dermis and sometimes the subcutis there are dilated capillaries and venules. Vessels tend to be cavernous in the upper dermis, few in numbers in the deep dermis, and capillary-like in the subcutis. A pseudo-infiltrating pattern may be seen in the subcutis, but close inspection reveals an overall lobulated pattern (444). There may be thrombosis with secondary papillary endothelial hyperplasia. The vessels are lined by a single layer of endothelial cells without evidence of endothelial proliferation. Inflammatory cells, haemosiderin and fibrosis may be associated. Older lesions show prominent acanthosis, hyperkeratosis with crust and papillomatosis. Ulceration is sometimes present.

Differential diagnosis
Angiokeratoma may also show verrucous epidermal hyperplasia. Verrucous haemangioma differs from angiokeratoma by its large size, involvement of deep vasculature and the presence of vessels that usually vary significantly in size. Angiokeratomas also show a hereditary basis in some cases, are often multiple and show a predilection for the lower trunk, thigh and external genitalia (444).

Prognosis and predictive factors
VH has a propensity to recur locally (2489). The condition progresses over time, and superficial therapy has been reported to exacerbate spread (2560). This may be due, in large part, to the fact that size of the lesion is usually underestimated clinically (444). Recurrence may also be seen in skin grafts.
**Pyogenic granuloma**

**Definition**
Pyogenic granuloma (PG) are rapidly growing, mostly exophytic lesions which may ulcerate.

**Synonym**
Lobular capillary haemangioma

**Epidemiology**
An epidemiologic study of 325 cases, (959) showed that 86% of the lesions were cutaneous, while only 12% of the cases affected mucosa. Overall, male patients outnumbered female patients. Pyogenic granuloma is especially common in children and young adults and the peak incidence is around the second decade of life.

**Etiology**
Most authors consider PG to be a hyperplastic rather than a neoplastic process (598,1615). Most lesions develop at sites of superficial trauma; in some cases lesions of PG are associated with endocrine alterations or medication and usually regress upon cessation of the stimuli.

**Localization**
PG preferentially affects the gingiva, lips, mucosa of the nose, fingers, and face (1247,1619), but examples of pyogenic granuloma have been described in all parts of the skin and mucous membranes including vulva, scrotum, penis, and glans penis (10,929,1477,2360).

**Clinical features**
PG presents typically as a papule or polyp with a glistening surface, which bleeds easily. Pyogenic granuloma usually develops at the site of a pre-existing injury. The lesions evolve rapidly over a period of weeks to a maximum size, then shrink and become replaced by fibrous tissue, which disappears within a few months. Epulis gravidarum a gingival lesion that develops during pregnancy, is the peak incidence is around the second decade of life. Lesions of PG recur they may show some atypical lesions which in some cases resemble an angiosarcoma especially in the deeper areas of the lesion. When lesions of PG develop within a vein, they are usually attached to the wall of the vein by a stalk and the lobular pattern is less prominent than in their extravascular counterparts.

**Histopathology**
Early lesions of pyogenic granuloma are identical to granulation tissue, containing, numerous capillaries and venules disposed radially to the skin surface, which is often eroded and covered with scabs. The stroma is oedematous and contains mixed inflammatory infiltrates with lymphocytes, histiocytes, plasma cells, neutrophils and an increased number of mast cells. Fully developed lesions of pyogenic granuloma are polyoid and show a lobular pattern with fibrous septa intersecting the lesion; hence the name lobular capillary haemangioma used by some authors for lesions at this stage. Each lobule is composed of aggregations of capillaries and venules lined by plump endothelial cells. At this stage most lesions have entirely re-epithelialized, and the epidermis forms collarettes of hyperplastic adnexal epithelium at the periphery, partially embracing the lesion; inflammatory infiltrates are sparse and the oedema of the stroma has disappeared. In the late stages of pyogenic granuloma there is a steady increase in the amount of fibrous tissue, so as the fibrotic struts widen, the lobules of capillaries become smaller and, with time, pyogenic granuloma evolves into a fibroma. When the specimen is deep enough, a small feeding artery and one or more veins may be seen ascending from the subcutaneous fat throughout the reticular dermis to directly enter the base of a pyogenic granuloma. The histopathological findings are the same in all variants of pyogenic granuloma. Uncommon histopathological features in lesions of pyogenic granuloma include intravascular papillary endothelial hyperplasia {1103} and extravascular haematopoiesis {1986}. When the lesions of PG recur they may show some atypical

**Immunohistochemistry**
PG lesions express factor positivity in the endothelial cells lining large vessels, but are negative in the cellular areas (346), whereas Ulex europaeus I lectin binds to the endothelial cells in both large vessels and cellular aggregates (1606). There is also expression of inducible nitric oxide synthase (2169), increased expression of vascular endothelial growth factor (298), low apoptotic rate expression of Bax/Bcl-2 proteins (1682), and strong expression of phosphorylated mitogen activated protein kinase (79) in lesions of pyogenic granuloma.

PCR investigations for human papillomavirus (1615) and human herpes virus type 8 (HHV8) (598) have yielded negative results.

**Prognosis and predictive factors.**
Lesions of PG are benign and easily removed by electrodesiccation and curettage; however lesions may recur, especially in those cases in which the proliferating vessels extend deep within the reticular dermis.

**Cavernous haemangioma**

Until a few years ago, the term “cavernous haemangiomas” was used to designate venous malformations. These lesions were also erroneously considered to be neoplasms, when in reality they are vascular malformations. They consist of slow-flowing, haemodynamically inactive vascular malformations, which are present at birth and slowly but progressively worsen throughout the lifetime of the patient. In some cases the lesions form a continuum of localized venous malformations, which include blue capillary spongy blebs, “cavernous” lesions (in which the venous lacunae are connected to the venous circulation by capillaries), localized saccular anomalies (connected by veins to the venous circulation) and diffuse venous ectasias. Many of the apparently localized and
superficial venous lesions tend to coexist with venous ectasias and deep vein anomalies.

**Angiokeratomas**

**Definition**
Angiokeratomas are acquired vascular lesions that result from the ectatic dilatation of pre-existing vessels in the papillary dermis, accompanied by hyperkeratotic epidermis (1101). Four clinical variants of angiokeratomas have been recognized, these are: solitary, angiokeratoma corporis diffusum, Mibelli and Fordyce.

**Epidemiology**
Solitary angiokeratomas affect mainly young adults. Angiokeratoma of Fordyce affects elderly people (34), however, there are examples of congenital cases (768). Mibelli angiokeratomas usually appear in childhood or adolescence and they are more common in females (986). Angiokeratomas of Fabry disease usually appear shortly before puberty and as an X-linked disease, they exclusively affect males; females may be asymptomatic carriers. Fabry disease is a rare error of the metabolism that results in a deficiency of the lysosomal enzyme hydrolase alpha-galactosidase A. It is transmitted as an X-linked recessive trait, alpha-galactosidase A has been localized to the middle of the long arm of the X chromosome (250,770).

**Etiology**
Solitary angiokeratomas are thought to be the result of injury, trauma, or chronic irritation to the wall of a venule in the papillary dermis.

Fordyce angiokeratomas are usually associated with varicocoele, inguinal hernia and thrombophlebitis (1788). The lesions may develop after surgical injuries to the genital veins (857); and there have been cases of angiokeratomas involving the glans penis mucosa of young patients developing after circumcision surgery (249). Similar lesions have been described in the vulva of young females (403,857). These lesions are thought to be the result of increased venous pressure that occurs during pregnancy or develops secondarily to the use of contraceptive pills.

Mibelli angiokeratoma is a condition that is inherited in an autosomal dominant fashion. Angiokeratoma corporis diffusum is the most unusual variant of all the angiokeratomas. It represents a cutaneous manifestation of a group of hereditary enzymatic disorders, but there is also an idiopathic form that presents with no other associated anomalies. Fabry disease is the disease most commonly associated with angiokeratoma corporis diffusum.

**Localization**
Solitary angiokeratomas may affect any anatomic site, including the oral cavity, although the lower limbs are the most frequent location (1101). Fordyce angiokeratomas are most common in the scrotum and vulva. Mibelli angiokeratomas usually affect the dorsum of the fingers, toes and interdigital spaces. Lesions of angiokeratoma corporis diffusum in Fabry disease affect the lower part of abdomen, genitalia, buttocks, and thighs in a bathing-trunk distribution.

**Clinical features**
Although their biologic significance varies greatly, angiokeratomas range from lesions that have very little clinical repercussion to widespread eruptions that are a manifestation of potentially fatal, systemic, metabolic diseases. Solitary angiokeratomas consist of small, warty, black, well-circumscribed papules. Sometimes solitary angiokeratomas develop thrombosis and recanalization with the development of secondary intravascular papillary clinically endothelial hyperplasia. Due to their colour, these lesions may be clinically confused with malignant melanoma (857). Fordyce angiokeratoma is characterized by the presence of multiple purple to dark papules, measuring 2-4 mm in diameter. In Mibelli angiokeratoma, the lesions consist of several dark papules with a slightly hyperkeratotic surface, and may be associated with acrocyanosis and chilblains. In rare instances, ulceration of the fingertips may appear as a complication of Mibelli angiokeratoma (592). Lesions of angiokeratoma corporis diffusum are small punctate dark red papules, some of them less than 1 mm in diameter. A frequent and asymptomatic finding is the so-called cornea verticillata, which is a superficial corneal dystrophy. This finding is of diagnostic importance for the detection of mild cases and female carriers. Other cutaneous manifestations include dry skin, anhidrosis, hyperthermic crises (1198), and acropaesthesiae secondary to capillary changes in the nail matrix (1132). In rare instances patients with Fabry disease may also present with concurrent Klippel-Trenaunay-Weber syndrome (821). Patients with Fabry disease who are devoid of cutaneous lesions have been reported (497). Angiokeratoma corporis diffusum is not exclusive to Fabry disease and has also been described in association with other rare inherited lysosomal storage diseases. By the same token, rare cases of angiokeratoma corporis diffusum have been described in patients without metabolic anomalies (565,1518). In some of these patients the angiokeratomas were multiple and presented in a zosteriform distribution.

**Histopathology**
All variants of angiokeratomas are identical under a conventional microscope. Common features of all angiokeratomas include the presence of dilated thin-walled blood vessels, lined by a layer of endothelial cells, in the papillary dermis and a variable degree of hyperkeratosis (1101). Occasionally, angiokeratomas may be seen overlying deep vascular malformations (1323). Hyperkeratosis is absent in Fordyce angiokeratomas and in angiokeratoma corporis diffusum (Fabry disease). In patients with Fabry disease there is vacuolization of the cytoplasm of the endothelial cells of the arterioles and smooth muscle cells of the arrector pili. The presence of these vacuoles may be a clue to the specific diagnosis in sections stained with haematoxylin and eosin. However, in most cases the amount of glycolipid in the skin is small making it extremely difficult, if not impossible to identify them, in routinely prepared sections. Special stains such as Sudan black B and PAS highlight the presence of glycolipid deposits within the vacuoles in patients with Fabry disease and related disorders. The lipid material is double refractile, which can be demonstrated by means of polaroscopic examination of unfixed, or formalin fixed frozen sections. Deposits of glycolipids in Fabry disease are not restricted to the lesions of angiokeratoma, but may also be seen in skin that appears to be normal.
Electron microscopy
Ultrastructural studies in angiokeratomas have demonstrated quantitative alterations of cytoplasmic organelles within the endothelial cells (833). Electron microscopy examination of the skin in Fabry disease show large electron dense lipid deposits in endothelial cells, pericytes, fibroblasts, arrector pili muscles and in secretory, ductal, and myoepithelial cells of the eccrine glands (1683). These deposits show a characteristic lamellar structure (1366,2438), not seen in other types of angiokeratomas or in lesions of angiokeratoma corporis diffusum with no enzymatic anomalies. Other ultrastructural findings in patients with Fabry disease consist of intersecting short crescent shaped, tightly packed membranes in the endothelial cells of the small cutaneous blood vessels (679) and cytoplasmic vacuoles in the epithelial cells of the eccrine glands (1094).

Arteriovenous haemangioma

Definition
Arteriovenous haemangiomas are benign, asymptomatic vascular proliferations. They are not associated with significant arterio-venous shunting.

ICD-O code 9123/0

Synonyms
Cirsoid aneurysm, acral arteriovenous tumour (384,385,528,1811).

Epidemiology
It occurs mainly in middle-aged adults, with no sex predilection.

Localization
Arteriovenous haemangioma is a neoplasm mainly affecting facial skin. Intraoral and vulvar examples have been also described (1318,1376,1698,1972).

Clinical features
Arteriovenous haemangioma presents as a red, purple, or skin coloured asymptomatic papule measuring 0.5-1.0 cm. Usually the lesions are solitary, although multiple examples have been cited. When the lesions are multiple they tend to cluster. Occasionally, they are associated with other abnormalities including epidermal naevus syndrome, vascular hamartomas and malformations (372).

Several examples of multiple arteriovenous haemangiomas have been described in patients with chronic liver disease (47).

Macroscopy
Grossly, lesions of arteriovenous haemangioma present as raised papules and on sectioning there is an admixture of white and red to brown areas, which represent the walls of the thick blood vessels containing blood.

Histopathology
Arteriovenous haemangioma is a well-circumscribed vascular proliferation that involves the upper and mid reticular dermis. The neoplasm is composed mainly of thick-walled muscle-containing blood vessels, lined by a single layer of endothelial cells. Intermingled with the thick-walled blood vessels are thin-walled dilated blood vessels and variable amounts of mucin. Although the thick-walled blood vessels resemble arteries, they lack a well-formed elastic internal membrane, and most likely represent ectatic veins (1318). In about one-fourth of the studied cases it is possible to identify both the arteriovenous shunts and the spiralled ascending small muscular artery (“feeder” vessel) with serial sections (834). The lesions recently described as symplastic haemangioma probably represent ancient arteriovenous haemangiomas with atypical cells due to degenerative changes that occur in long-standing lesions (1351).

Histogenesis
The precise nature of arteriovenous haemangioma is uncertain. Initially it was considered to be a multicentric hamartoma of the sub-papillary vascular plexus with one or more arteriovenous anastomoses (834). Other authors have suggested that a hamartoma of the Sucquet-Hoyer canal of the glomus body is the cause of this lesion. The latter interpretation, however, is unlikely because glomus cells are usually absent in arteriovenous haemangioma, and to date, they have been identified in only one example of all the reported cases (1318).

Prognosis
Arteriovenous haemangioma is a benign lesion and local excision suffices.

Cutaneous angiosarcoma

Definition
Angiosarcoma is a malignant neoplasm of endothelial cells. Differentiation between lymphangiosarcoma and sarcomas with blood vascular differentiation appears problematic at the current time.
ICD-O code 9120/3

Synonyms
Lymphangiosarcoma, haemangiosarcoma.

Epidemiology
There are low-grade forms of angiosarcoma that can occur outside the circumscribed clinical settings detailed herein. Almost all high-grade angiosarcomas are in one of the following settings: the head and neck of predominantly male elderly patients (the most common setting) (1046), the chest of patients who have undergone mastectomy for breast cancer (Stewart-Treves syndrome) (2269), lymphoedema (congenital or acquired), or post-irradiation (2271).

Localization
Most of the epidemiologic settings also define the sites of disease.

Clinical features
Angiosarcoma, regardless of its genesis usually begins as a very poorly defined red plaque resembling a bruise (1046). Lesions can become quite large before metastasis occurs. When it does, the spread is usually haematogenous. Its borders may extend for several centimetres beyond what is visible (1969). Areas of nodularity arise after a time, but not in all patients. Unless a lesion is detected very early, multiple relapses and death are frequent occurrences.

Histopathology
Angiosarcoma begins as a plaque, with small, jagged thin walled vessels that insinuate themselves between collagen bundles of the reticular dermis. Unlike in Kaposi sarcoma, there is no tendency of spindled cells to first appear in increased number around pre-existent vessels and/or adnexa. The endothelial cells become progressively more protuberant, with enlarged, hyperchromatic nuclei. Lymphoid nodules are sometimes seen. The edges of plaques of angiosarcomas can be very poorly demarcated, making it practically impossible to provide accurate information about the resection margins. Plaques of spindled endothelial cells in the post-mastectomy setting are not necessarily those of angiosarcoma, as Kaposi sarcoma can also occur (59). The plaque stage of angiosarcoma can give rise to nodules, composed of compact masses of spindled or epithelioid cells, or both. Vascular lumina may be hard to detect in such nodules, and careful inspection may be needed to differentiate these from melanoma and spindle cell squamous carcinoma if only a partial biopsy is submitted. Cytoplasmic vacuoles may be a clue to endothelial differentiation in poorly differentiated cases.

Immunohistochemistry
The cells of angiosarcoma are usually positive for CD31, CD34 or VWF(VIIIrAg). Poorly differentiated tumours can lose one or more of these antigens, necessitating a panel in difficult cases (1755). Recently FLI-1 has been described as a useful marker with the additional advantage of nuclear staining (761). Angiosarcoma in the post-mastectomy setting may show blood vascular differentiation, despite a pathogenesis related to lymphoedema (1277). Angiosarcomas are consistently negative for HHV-8 (1371).

Differential diagnosis
It includes the atypical vascular proliferation after radiation therapy, Kaposi sarcoma and pseudovascular squamous cell carcinoma.

Genetics
Cytogenetic changes include gains of 5pter-p11, 8p12-qter, and 20pter-q12, losses of 7pter-p15 and 22q13-qter, and −Y (2101). Insufficient numbers of cases have been analyzed to determine if there are reproducible differences between different types of angiosarcoma.

Prognosis and predictive factors
Metastases to regional lymph nodes and to the lungs occur, often after repeated local recurrences and surgical excisions. The prognosis is poor, and in one series, only 15% of patients survived for 5 years or more after diagnosis (1046). This, in part, reflects the delayed diagnosis of these lesions. This limited survival is despite the use of various treatment modalities, sometimes involving surgery, radiotherapy, and chemotherapy.
Lymphangioma circumscriptum

Definition
Lymphangioma circumscriptum refers to a vascular malformation involving the lymphatic vessels of the superficial dermis. A denomination as superficial lymphatic malformation would be more appropriate to describe this lesion.

ICD-O code 9170/0

Epidemiology
Usually, lymphangioma circumscriptum is present at birth or appears early in life.

Localization
Lymphangioma circumscriptum may be located in any anatomic site, but has predilection for the axillary folds, shoulders, neck, proximal parts of the extremities and tongue (750,1798,2502). Lesions involving eyelids and conjunctiva (841) and genital skin of males and females (149,419,2006,2436) have also been described.

Clinical features
Clinically, the lesion consists of numerous small vesicle-like lesions, often with a verrucous surface, grouped in a plaque. Sometimes purplish areas within the lesion are seen due to haemorrhage and thrombus formation within the blood vessel component. Probably, the superficial vesicles are the result of saccular dilatations of superficial lymphatics secondary to raised pressure transmitted from the underlying pulsating cisterns (2502). Magnetic resonance imaging accurately demonstrates the true extent of involvement (1541). In rare instances, superficial lymphatic malformations are associated with visceral lymphatic malformations involving the mediastinum (1643) or the bladder wall (1107). Additional associations include Becker naevus (1762), and superficial lymphatic malformations have been described in patients with Maffucci syndrome (2292) and Cobb syndrome (2168).

Macroscopy
The excised specimens of lymphangioma circumscriptum show dilated vascular spaces involving both the superficial dermis and deeper subcutaneous tissue, which correspond to the malformed lymphatic vessels.

Histopathology
The stereotypical superficial lymphatic malformation is accompanied by deep lymphatic dilated cisterns with muscular walls situated in the subcutaneous fat, resulting in swelling of the tissue beneath the superficial vesicles (1768). The superficial component consists of dilated lymph vessels, lined by flat endothelial cells in a discontinuous layer, and situated in the papillary dermis, and the superficial reticular dermis (179,750). Sometimes, the lymphatic vessels are arranged in clusters in the papillary dermis, resulting in a papillated or verrucous skin surface. The vessels may contain homogeneous eosinophilic proteinaceous lymph or blood, and occasionally foamy macrophages. Scattered lymphocytes may be seen in the connective tissue stroma between dilated lymphatic vessels. In extensive lesions, large irregular lymphatic channels are usually seen beneath the superficial vessels in deep reticular dermis and subcutaneous fat.

Immunohistochemistry
The usual immunohistochemical markers for endothelial cells, such as factor VIII-related antigen, Ulex europaeus, and CD31 do not differentiate between blood and lymphatic vessels (1799). In these cases, new endothelial cell markers such as vascular endothelial growth factor receptor-3 (VEGFR-3) (763,1463), D2-40

Fig. 5.15 Lymphangioma circumscriptum. A Close-up view of the lesions showed that it consisted of numerous vesicle-like lesions, some of them with a verrucous surface, grouped in a plaque. Purplish areas are seen due to haemorrhage and thrombus formation within a blood vessel component. B Histopathologically, the lesion consisted of dilated lymph vessels involving the superficial dermis and covered by hyperplastic epidermis with compact hyperkeratosis.

L. Requena
W. Weyers
C. Díaz-Cascajo
Prox1 (2535) may be helpful, since these markers are expressed by lymphatic endothelium (763,1463).

**Histogenesis**
Lymphangioma circumscriptum results from abnormalities in the embryologic development of lymphatic vessels of the skin. Lymphangioma circumscriptum probably represents sequestrated dermal lymphatic vessels that failed to link up with the rest of the lymphatic system (2502). However, an ultrastructural study suggested that lymphangioma circumscriptum was induced by long-standing lymphatic stasis (103). In some patients, lymphangioma circumscriptum has developed after surgery or radiotherapy on the involved area (1406,1859).

**Prognosis and predictive factors**
Usually, lymphangioma circumscriptum is a localized and superficial lymphatic malformation that only causes cosmetic problems and does not require treatment. The presence of a deep component may explain the tendency of the lesions to persist after superficial excision.

**Progressive lymphangioma**

**Definition**
Progressive lymphangioma is a benign, localized, slow-growing neoplasm composed of thin-walled, interconnecting vascular channels in the dermis and subcutis.

**ICD-O code**
9170/0

**Synonyms**
Acquired progressive lymphangioma, benign lymphangioendothelioma.

**Epidemiology**
Progressive lymphangioma is rare. It occurs chiefly in middle-aged or older adults and does not show a sex predilection (918).

**Etiology**
 progress. Progressive lymphangioma has been reported after trauma, such as surgical procedures and tick bites. Inflammation secondary to trauma has been claimed to play a role (2463,2532).

**Localization**
Lesions have been reported most commonly on the lower extremities, but any region of the skin may be affected (918).

**Clinical features**
Lesions usually present themselves as solitary, well-circumscribed, red or violaceous patches or plaques. Although usually asymptomatic, patients may complain of tenderness, pain, or itching. Because of slow growth over years, lesions may measure several centimetres in diameter (918,1157).

**Histopathology**
Progressive lymphangioma is characterized by delicate, often widely dilated vascular spaces lined by a monolayer of monomorphous endothelial cells. In some foci, endothelium-lined papillary stromal projections extend into those spaces. With progressive extension into the deep dermis, vascular spaces become narrower. They tend to dissect between collagen bundles and to surround pre-existing vessels and adnexal structures. Endothelial cells are more numerous than in normal lymphatic vessels and may be closely crowded together. Nuclei may be hyperchromatic, but there is no prominent nuclear atypia.

**Immunohistochemistry**
Endothelial cells are usually stained by antibodies against CD31 and CD34, whereas other endothelial markers give more inconsistent results. Actin-positive pericytes around vascular lumina are present focally (918,1157).

**Differential diagnosis**
Lymphangioma-like Kaposi sarcoma dif-
fers from progressive lymphangioma by the presence of plasma cells, the invariable presence of HHV-8 and more classic areas of Kaposi sarcoma elsewhere in the lesion. The so-called atypical vascular proliferation following radiotherapy (benign lymphangiomatous papules) differs from progressive lymphangioma clinically and histopathologically by presenting as tiny vesicles and histopathologically by being associated with much wider spaces in the upper dermis. Moreover, these lesions are thought to represent lymphangiectasias, rather than a neoplastic process (628, 1921).

Histogenesis
Progressive lymphangioma is considered to be a neoplastic proliferation of lymphatic vessels. A neoplastic nature is suggested by its slowly progressive course. Derivation from lymphatic endothelia has been suggested on the basis of rare erythrocytes within and around vascular lumina and absence of a peripheral ring of actin-positive pericytes in most vessels.

Prognosis and predictive factors
Following surgical excision, local recurrences are exceptional. Metastases do not occur. Regression of lesions after systemic therapy with corticosteroids and in the absence of any treatment has been reported (918, 1577, 2463).

Lymphangiomatosis
Definition
Lymphangiomatosis is characterized by a diffuse proliferation of lymphatic vessels that may involve bones, parenchymal organs, soft tissue, and skin.

Synonyms
Generalized lymphangioma, systemic cystic angiomatosis, multiple lymphangiectasias.

Epidemiology
Lymphangiomatosis is a rare disease occurring mainly in the first two decades of life. There seems to be no sex predilection (862, 1882).

Localization
Lesions occur in the skin and the superficial soft tissues of the neck, trunk, and extremities. Most cases of lymphangiomatosis affect bones and parenchymal organs, especially the lung, pleura, spleen, and liver. Soft tissue involvement occurs in the mediastinum and retroperitoneum.

Clinical features
Cutaneous and subcutaneous lesions present themselves as soft, fluctuant swellings that can be squeezed from one area to another and that may be associated with tiny vesicles. In patients with involvement of bones and visceral organs, the presenting signs range from pathologic fractures to chylothorax, chyloous ascites, and other symptoms related to particular organs affected by the process. The interconnected lymphatic channels can be visualised by lymphangiography or direct injection of contrast media into cystic vascular spaces. Plain x-rays often reveal osteolytic areas as a consequence of involvement of bones (862, 1882).

Histopathology
Cutaneous lesions of lymphangiomatosis are characterized by markedly dilated lymphatic channels throughout the skin and subcutis that are lined by a single attenuated layer of flattened endothelial cells and usually appear empty. Those channels tend to dissect between collagen bundles and to surround pre-existing structures in a manner reminiscent of well-differentiated angiosarcoma. Unlike angiosarcoma, cytologic atypia, endothelial multilayering, and mitotic figures are absent. The stroma often contains numerous siderophages and focal aggregates of lymphocytes. Exceptionally extramedullary haematopoiesis may be seen.

Histogenesis
Lymphangiomatosis probably represents a vascular malformation, rather than a neoplastic process.

Prognosis and predictive factors
When present on the neck and trunk, lymphangiomatosis of soft tissues is usually associated with extensive osseous or visceral involvement and carries a grave prognosis with a high rate of mortality (1882). In lymphangiomatosis of the limbs, involvement of bones and visceral organs is usually insignificant and prognosis, therefore, favourable (1021).
Smooth muscle is found in the skin in the arrector pili muscles, the walls of blood vessels and in ‘genital’ skin, which includes the scrotum (dartos muscle), vulva and nipple (areolar smooth muscle). Each of these sites of smooth muscle can give rise to a tumour. Tumours of striated muscle are exceedingly rare in the skin. Only the rhabdomyomatous mesenchymal hamartoma (striated muscle hamartoma) will be considered below.

Smooth muscle hamartoma

Definition
Smooth muscle hamartoma is a proliferation of dermal smooth muscle bundles that is usually congenital.

Synonyms
Arrector pili hamartoma, congenital pilar and smooth muscle naevus, congenital smooth muscle naevus

Epidemiology
Smooth muscle hamartoma is usually congenital with only occasional reports of lesions with onset in adolescence or adulthood (590,1069). There is a slight male predominance. The lesion is uncommon (1028).

Localization
The lesions are most often located on the trunk and extremities, particularly proximally (1145). Cases have been reported involving the head and neck region (1290), scrotum (1870) and conjunctiva (1966).

Clinical features
The typical presentation is as a solitary patch or plaque of varying size, usually between 1 and 10 cm, which may show hyperpigmentation and/or hypertrichosis (1145) and which may increase in size with the growth of the patient (2610). A positive pseudo-Darier sign is seen in most cases (2610). Occasional cases have an atrophic appearance (886). Less common presentations may include papular follicular lesions (659), multiple lesions (915,2200) and the so-called "Michelin tyre baby", the latter typically in boys. Patients with Michelin tyre syndrome may have various other associated abnormalities (2093). A clinical classification has been proposed in which type 1 refers to the usual localized form, type 2 the follicular variant, type 3 to multiple lesions and type 4 to the diffuse variant (819).

Histopathology
There are increased numbers of variably orientated discrete smooth muscle bundles within the dermis and sometimes the subcutis and these may connect to hair follicles (1145,2093). The overlying epidermis may show acanthosis and basal hyperpigmentation and there may be prominent folliculosebaceous units present, although these do not appear to be increased in number (206,1145).

Immunohistochemistry
Lesions have been positive for smooth muscle actin and desmin as expected (886,1299,2093). CD34 positive dendrocytes have been reported to be an integral part of the proliferation (1299).

Differential diagnosis
Becker naevus may show dermal changes identical to smooth muscle hamartoma. It has been suggested that these lesions may form a spectrum (1145). Pilar leiomyoma differs from smooth muscle hamartoma in being acquired, frequently multiple, often painful and comprising less discrete smooth muscle bundles with intervening collagen.

Genetic susceptibility
Rare cases of smooth muscle hamartoma have been described in siblings and in a mother and her children (915). Xp microdeletion syndrome is characterized by an unbalanced translocation between the X and Y chromosomes leading to deletion of the distal short arm of the X chromosome. Affected infants show microphthalmia, linear skin defects and sclerocornea. The linear skin defects have been reported to show histological features similar to smooth muscle hamartoma (1794) although this was not described in another case (686). A child with a familial paracentric inversion of chromosome 7q and Michelin tyre syndrome with smooth muscle hamar-
toma has been described. The relevance, if any, of the genetic abnormality is unknown {2093}.

**Pilar leiomyoma**

**Definition**
Pilar leiomyoma is a benign tumour derived from the arrector pili muscle (1054,1878).

**ICD-O code** 8890/0

**Synonym** Piloleiomyoma

**Epidemiology**
Solitary lesions have a female preponderance. They usually develop in adult life. Rarely, they are present at birth. Multiple lesions usually have their onset in the late second or third decades of life.

**Localization**
Solitary lesions may develop anywhere on hair-bearing skin, particularly the trunk and limbs. Multiple lesions have a predilection for the face, back and extensor surfaces of the extremities.

**Clinical features**
Pilar leiomyomas may be solitary or multiple, with up to several hundred lesions. Multiple lesions may be grouped, linear, or zosteriform. Solitary lesions may measure up to 2 cm or more in diameter, but multiple lesions are much smaller. Leiomyomas are firm reddish-brown papulonodules. Multiple lesions are usually painful; solitary lesions are infrequently so.

**Histopathology**
Pilar leiomyomas are circumscribed (but not sharply so), non-encapsulated tumours of the dermis, composed of bundles of smooth muscle arranged in an interlacing or haphazard pattern. The cells have abundant cytoplasm and elongated nuclei with blunt ends. Mitoses are infrequent or absent (1878). Atypical cells, similar to those seen in the symplastic leiomyoma of the uterus, are uncommon (1486). Granular cell variants are extremely rare (1586). Small amounts of fibrous stroma are present between the muscle bundles in older lesions, but there is usually less stromal collagen than in the smooth muscle hamartoma. Overlying epidermal hyperplasia is sometimes present (1878). The tumour cells stain for desmin and smooth muscle actin.

**Genetics**
Some of the multiple cases are familial, with an autosomal dominant inheritance (728). The syndrome of multiple cutaneous and uterine leiomyomas is also autosomal dominant with the locus on chromosome 1q42.3-q43 (51,1526).

**Cutaneous leiomyosarcoma**

**Definition**
Cutaneous (dermal) leiomyosarcoma is a malignant neoplasm of smooth muscle cells arising in the dermis. Subcutaneous and soft tissue leiomyosarcomas are discussed in the soft tissue monograph.

**ICD-O code** 8890/3

**Epidemiology**
Over 100 cases of dermal leiomyosarcoma have now been reported (1164). Most cases develop in adults, with a peak incidence in the sixth decade. Childhood cases are extremely rare (2563). There is a male predominance.

**Localization**
These tumours have a predilection for the extensor surfaces of the extremities and to a lesser extent the scalp and trunk (593).

**Clinical features**
Dermal leiomyosarcomas are solitary, firm nodules measuring 0.5-3 cm in diameter. They are usually asymptomatic, but pain and tenderness have been recorded.

**Histopathology**
By definition, the major portion of the tumour is in the dermis, although subcutaneous extension is present in some cases. They have an irregular outline with tumour cells infiltrating into, or blending with the collagen fibres at the periphery. The tumour is composed of interlacing bundles of elongated spindle-shaped cells with eosinophilic cytoplasm and blunt-ended nuclei. Sometimes there is a suggestion of nuclear palisading. There is at least one mitosis per 10 high-power fields in cellular areas. Pockets of greater mitotic activity (mitotic ‘hot spots’) are found, usually in areas showing nuclear pleomorphism. Granular cell, epithelioid, inflammatory and desmoplastic variants have all been described (2476). Two different growth patterns have been described: A nodular pattern which is quite cellular with nuclear atypia and many mitoses; and a diffuse pattern which is less cellular with well-differentiated smooth muscle cells and inconspicuous mitoses (1164).

**Fig. 5.21** Leiomyosarcoma. confined to the dermis. There are bundles of spindle shaped cells and scattered mitotic figures. Not the nuclear pleomorphism.
Immunohistochemistry
The cells express smooth muscle actin. Desmin is present in the majority of cases. Pan-muscle actin (HHF-35) is sometimes present focally.

Histogenesis
The majority of tumours are derived from the arrector pili muscles. Rare cases derived from areolar smooth muscle in the nipple (1452) and dartos muscle in the scrotum (758) have been reported.

Genetics
An unequivocal genetic fingerprint for these tumours is currently lacking (2175). Various genes have been identified that are expressed differentially in tumour and normal tissue. Soft tissue leiomyosarcomas most often show genomic alterations in the 13q4-q21 region (622).

Prognosis and predictive factors
Dermal leiomyosarcomas may recur locally, but the reported incidence (5-30%) varies widely (2476), but metastases of confirmed cases are unknown (1139).

Rhabdomyomatous mesenchymal hamartoma
Definition
Rhabdomyomatous mesenchymal hamartoma (RMH) refers to single or multiple, congenital, frequently polyoid lesions that typically arise near the midline of the head and neck. They contain skeletal muscle fibres within the dermis (1618).

Synonyms
Striated muscle hamartoma (1008), congenital midline hamartoma.

Epidemiology
About 25 examples of this lesion have been reported (1973,2320). Typically, the lesions have been present since birth or early childhood, and most patients are children. Rare cases have been reported in adults (2037). Thus far, the male:female ratio is 2:1.

Etiology
These lesions may be derived from striated muscle of the branchial arch (105, 899,1008,1973).

Localization
RMH typically arises in the midline of the head and neck, with a particular predilection for the nose and chin. There have also been cases involving the preauricular region (1902,2010,2122), lateral forehead (1973), and cheek (2320).

Clinical features
The majority of lesions are described as papules or polyps, but a few have presented as nodules (105,1973,2320) or “sessile masses” (1685). RMH lesions are generally asymptomatic, but they can demonstrate the interesting property of contractile motion, spontaneously or during crying or feeding (1973,2010). Most patients lack other congenital anomalies, but there have been associations with cleft lip and palate, ocular abnormalities (coloboma, microphthalmia, limbal dermoid), low-set ears, craniofacial clefts, thyroglossal duct sinus, lipoma of the brain, and upper extremity and syndactyly (1008,1902,1973,2010,2037). Histologic features of RMH have been found in the cutaneous polyps (2037) of a case of Delleman syndrome, which consists of orbital cysts, cerebral malformations, and focal dermal hypoplasia as well as cutaneous appendages (723). In addition, a patient (1902) with RMH in association with ipsilateral limb malformation and coloboma (Goldenhar syndrome), has been reported.

Initially, it was believed that RMH might be an X-linked disorder, as the first few cases were reported in males, but this...
Varying amounts of collagen and mature fat surround these muscle fibres (2037). They extend through the reticular dermis and become attenuated in the papillary dermis (1618), where they appear to surround adnexal structures, particularly vellus follicles and sebaceous glands (678,713,1618). Sebaceous and eccrine sweat glands are usually observed, and in one case there were ectopic apocrine glands (2320). Nerve elements in these lesions vary considerably; in some cases they are not prominent (2010), but in others there may be numerous small nerve twigs (987) or a large nerve bundle in the central core of the lesion (2037). One example contained elastic cartilage (2037), and calcification or ossification have also been reported (2010). In some cases, elastic fibre distribution has been reported to be normal (1618), while in others these fibres are markedly decreased (2037).

**Immunoprofile**

Skeletal muscle fibres in RMH stain positively for actin, desmin and myoglobin (678,899).

**Differential diagnosis**

Although RMH bears a resemblance to fibroepithelial polyp, naevus lipomatosus, and accessory tragus, the combination of midline location and a microscopically skeletal muscle component should permit distinction from those lesions (though small amounts of skeletal muscle have been reported in accessory tragi) (324)). Deeper or more primitive tumours such as fetal rhabdomyoma, fibrous hamartoma of infancy, or neuromuscular hamartoma (benign Triton tumour) should not be difficult to distinguish from RMH (678,2010).

**Somatic genetics**

There has been speculation about a human homolog of the mouse disorganization gene (Ds), which is responsible, directly or indirectly, for the development of hamartomas and other defects (1973,2242).

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**Fig. 5.23** Rhabdomyomatous mesenchymal hamartoma. In the lower part, skeletal muscle fibres among thick collagen bundles of the reticular dermis. In the upper part there are eccrine sweat coils and aggregates of smooth muscle.
Keloid scar

Definition
Keloid scars are raised scars that extend beyond the confines of the original wound.

Epidemiology
Keloid scars occur with equal frequency in men and women. They affect all races, but are more common in dark-skinned individuals. In Black, Hispanic, and Asian populations, the incidence ranges between 4.5 and 16%. Keloids occur chiefly in persons under 30 years of age \(1711,2149\).

Etiology
There is a genetic predisposition to the formation of keloid scars. Moreover, hormonal and immunological factors may play a role. Keloids often appear in puberty and tend to enlarge during pregnancy; they have been claimed to be more common in patients with signs of allergy and increased serum levels of IgE. Wounds subjected to great tension or become infected are more likely to heal with a keloid scar \(1711,2149\).

Localization
Keloids are most common on the earlobes, cheeks, upper arms, upper part of the back, and deltoïd and presternal areas. They are seen only rarely on the genitalia, eyelids, and on palms and soles \(1711,2149\).

Clinical features
Keloids are well-circumscribed, firm, smooth-surfaced erythematous papules or plaques that occur at the site of an injury. The preceding injury may be only minor and, therefore, not always apparent (e.g., rupture of an inflamed hair follicle). Older lesions may be pale or hyperpigmented. Especially in early stages, keloids are often itchy, tender, or painful \(1711,2149\).

Histopathology
After a prolonged period of wound healing thick, homogeneous, strongly eosinophilic bundles of collagen, in haphazard array, develop \(1498\). Those “keloidal” collagen bundles are the histopathologic hallmark of keloid scars, but are not seen in many cases fulfilling the clinical definition of keloids. The border of keloids is often irregular, with tongue-like extensions of bands of thickened collagen underneath normal appearing epidermis and superficial dermis.

Histogenesis
Keloid scars are characterized by an enhanced proliferation and metabolic activity of fibrocytes that seems to result, in part, from the excess of various cytokines produced by inflammatory cells, including transforming growth factor-b1 and platelet-derived growth factor. Moreover, a deficiency of cytokines that down-regulate collagen synthesis and inhibit proliferation of fibrocytes, such as interferon-a, has been noted. There is also evidence of reduced degradation of collagen caused, in part, by inhibition of collagenase activity through acid mucopolysaccharides, proteoglycans, and specific protease inhibitors \(1686,1711,2149,2551\).

Genetic susceptibility
Keloidal scar formation may run in families. It is also more common in Black individuals. A relationship with various human leukocyte antigens has been reported \(1711\).

Prognosis and predictive factors
The clinical and histopathologic features of keloid scars indicate a high probability of recurrence following surgical excision alone. Recurrence rates of 45-100% have been described \(1711\).

Hypertrophic scar

Definition
Hypertrophic scars are raised scars that do not extend beyond the confines of the original wound. As such, they are closely related to keloids, both being examples of a disturbance of wound healing leading to the formation of exuberant fibrous tissue. Whether hypertrophic scars are simply a less severe variant of keloid scars or represent a different pathologic process is controversial.

Epidemiology
Hypertrophic scars are common. The incidence of hypertrophic scarring (including keloid scars) ranges between 39 and 68% after surgery and between 33 and 91% after burns, depending on the depth of the wound \(1711\).

Localization
Hypertrophic scars are most common above the flexor aspects of joints and on the abdomen \(2149\).

Clinical features
By definition, hypertrophic scars differ from keloid scars by remaining confined to the original wound. Other distinguishing features are earlier manifestation of...
hypertrophic scars (usually within 4 weeks after injury, whereas keloids may manifest themselves several months later), a tendency to regression and to contractures not seen in keloid scars, a lower tendency to recur after surgery, and different sites of predilection. In other respects, the clinical features of hypertrophic and keloid scars are essentially the same (2149).

**Histopathology**
Hypertrophic scars differ from normal scars chiefly by presence of nodular aggregates of collagen with many fibrocytes. The main distinguishing feature from keloid scars is the absence of keloidal (i.e., thick, strongly eosinophilic) bundles of collagen. Moreover, unlike keloid scars, hypertrophic scars show prominent blood vessels arranged perpendicularly to the skin surface. Borders of hypertrophic scars tend to be more regular, and nodules of collagen tend to be distributed more evenly.

**Differential diagnosis**
Keloids show thick hyaline collagen bundles. Cases with overlap features between keloids and hypertrophic scars are seen.

**Histogenesis**
No principal differences have been noted in the histogenesis of hypertrophic scars and keloid scars (1711).

**Prognosis and predictive factors**
Although hypertrophic and keloid scars are closely related, the distinguishing features, clinically and histopathologically, allow a judgment to be made about the probability of recurrence following surgical excision. In one series, the recurrence rate of hypertrophic scars was 10%, as opposed to 63% in keloid scars (257).

**Dermatomyofibroma**

**Definition**
Dermatomyofibroma is a distinct biologically benign fibroblastic/myofibroblastic cutaneous proliferation occurring frequently, but not exclusively in young female patients.

**ICO-O code**
8824/0

**Synonym**
Plaque-like dermal fibomatosis

**Epidemiology**
Dermatomyofibroma represents a relatively rare cutaneous mesenchymal neoplasm and usually occurs in young women. Infrequently, dermatomyofibroma is seen in male patients (1073,1189, 1581) and children (1654,1970).

**Localization**
Most cases of dermatomyofibroma arise in the shoulder and axilla regions, fol-
Infantile myofibromatosis

Definition
Infantile myofibromatosis (IM) is a tumour of the skin and soft tissues of disputed histogenesis, which is solitary in two thirds of cases. Multicentric lesions (myofibromatosis) occur (634A).

ICD-O code 8824/1

Synonyms
Solitary cutaneous myofibroma.

Historical annotation
IM was described by Chung and Enzinger in 1981 as a proliferative disorder of myofibroblasts (486). Cases had been described earlier as congenital fibrosarcoma (2529), congenital generalized fibromatosis (1229) and congenital mesenchymal hamartoma (203).

Epidemiology
Most lesions are present at birth, or appear in the first 2 years of life; onset in adults also occurs (2541). There is a male predominance.

Clinical features
About a third of lesions are situated in the deep soft tissues and the remainder are located in the skin and/or the subcutaneous tissues (1778). The head, neck and trunk are the usual sites.

They measure 0.5 to 7 cm or more in diameter; they are greyish-white in colour, and fibrous in consistency.

Histopathology
The nodules are reasonably well circumscribed, although there be an infiltrative border in the subcutis. There are plump to elongated spindle cells, grouped in short fascicles. Delicate bundles of collagen separate or enclose the cellular aggregates. Mitoses are variable in number, but not atypical (486,753).

Vascular spaces resembling those seen in haemangiopericytoma are often found in the centre of the tumour, giving a biphasic appearance. Necrosis, hyalinization, calcification, and focal haemorrhage may be present centrally (753). For details, see WHO Classification of Tumours of Soft Tissue and Bone (756).

Immunoprofile
The tumour cells are positive for vimentin and alpha-smooth muscle actin, but negative for S-100, myoglobin, and cytokeratins (2425). Reports on immunoreactivity for desmin vary (923).

Histogenesis
Fletcher and colleagues have suggested that the spindle cell component shows smooth muscle differentiation (753). Requena et al have suggested an origin from myopericytes. (1920). Recently, the lesion has been included in a spectrum of tumours showing perivascular myoid differentiation (882).

Genetics
Familial occurrence is too rare to allow any conclusions regarding genetic susceptibility (2427).

Prognosis
The prognosis is excellent, with recurrence unlikely after excision; aggressive variants are rare (849). There are no features predictive of recurrence.

Sclerotic fibroma

Definition
Sclerotic fibroma is a benign soft tissue tumour composed of eosinophilic collagen bundles arranged in a storiform pattern (1895).

ICD-O code 8823/0

Synonym
Storiform collagenoma

Epidemiology
Solitary sclerotic fibroma is rare and occurs in both sexes at any age, from infancy to adulthood. Multiple tumours are typical of Cowden disease, a rare genodermatosis.

Localization
Most frequent sites of involvement are the face, upper and lower extremities and trunk.

Clinical features
Sclerotic fibroma presents as a translucent, white, flesh-coloured or waxy nodule. It is usually unique and measures less than 1 cm. It has a slowly progressive growth, over months or years. The lesion is asymptomatic (1590,1895, 2369).
**Histopathology**
The tumour is usually situated in the reticular dermis. It is sharply demarcated and it is composed of hyalinized bands of collagen with a decreased number of fibroblasts. The collagen fibres are thick, glassy and aligned in parallel bundles with a storiform pattern. Elastic fibres are absent. The proliferation tends to expand, pushing aside the normal dermal collagen without engulfing the adnexae (1590,1895,2369). Alcian Blue staining reveals an increased amount of mucopolysaccharide.

**Immunoprofile**
Staining for S100 protein, myelin basic protein and neuron specific enolase and desmin are negative (1590,1895).

**Prognosis and predictive factors**
Although the lesion is benign, it should be removed due to its tendency to expand.

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**Digital mucous cyst**

**Definition**
Two types of lesions both with a pseudocystic circumscribed dermal mucin deposition exist. In the more common type a connection with the underlying joint cavity can be demonstrated (ganglion type). The second type represents a focal mucinosis produced by fibroblasts (myxomatous type).

**Synonyms**
Myxoid pseudocysts of the digits, ganglion of the distal interphalangeal joint, digital focal mucinosis.

**Epidemiology**
Women are more often affected and patients are middle aged or elderly.

**Localization**
They typically occur on the dorsum of the fingers near the distal interphalangeal joint or near the proximal nail fold. The index fingers and thumb are primarily affected. The toes are rarely involved (1148,2221).

**Clinical features**
The lesions are solitary, soft, smooth surfaced and usually not greater than 1.5 cm. A connection of the pseudocyst to the underlying joint can be demonstrated in the majority of cases by magnetic resonance imaging or injection studies with dye (599,1034). Osteoarthrosis is sometimes evident.

**Histopathology**
Myxomatous type: this variant has a large pseudocystic area with a myxomatous stroma with scattered spindle-shaped or stellate fibroblasts analogous to focal mucinosis in other areas of the body. The overlying epidermis is often attenuated. The mucin contains mucopolysaccharides which stain positively with alcian blue and colloidal iron. Ganglion type: cystic spaces containing mucin with a collagenous fibrous wall characterize these lesions. Occasionally in some areas of the wall a synovial lining can be demonstrated.

**Digital fibrokeratoma**

**Definition**
Digital fibrokeratoma is a benign fibrous tumour often accompanied by a hyperplastic epidermis that arises mostly in the periungual area.

**Synonyms**
Acquired ungual fibrokeratoma, periungual fibromas of tuberous sclerosis (Koenen tumours), subungal and periungual fibromas, acral fibrokeratoma.

**Epidemiology**
Most patients are adults. Males are affected more frequently than females (2429). More than half the patients with tuberous sclerosis develop about puberty multiple fibrokeratomas (2470).

**Localization**
The majority of lesions occur on a finger or a toe. Occasionally, lesions present on the palms or soles.

**Clinical features**
The patients usually present with a solitary lesion. Normally, tumours are small and measure 3-5 mm in diameter. A case of a huge lesion measuring up to 5 cm has been described (1181).

**Histopathology**
Digital fibrokeratoma is composed of dense collagen fibres, often with vertical orientation, with a variable number of mature fibroblasts and small blood vessels. A few inflammatory cells can be observed. There is often epidermal hyperplasia. In the stroma thin elastic fibres are present and hair follicles are absent. In a rare variant an oedematous and less dense stroma is found (1279,1280).

**Genetics**
In patients with tuberous sclerosis mutations in two different genes, TSC1 on
chromosome 9 and TSC2 on chromosome 16 have been identified (582).

**Pleomorphic fibroma**

**Definition**

Pleomorphic fibroma (PF) is a benign, polypoid or dome-shaped cutaneous neoplasm with cytologically atypical fibrohistiocytic cells (1188).

**ICD-O code**

8832/0

**Epidemiology**

PF occurs mostly in adults (39,1188).

**Localization**

They are located on the trunk, extremities, head (39,1188) and rarely the subungal region (983).

**Clinical features**

PF are asymptomatic, solitary, slowly growing, flesh coloured and non-ulcerated dome-shaped to polypoid papules from 4-16 mm. The clinical differential diagnosis includes acrochordon, neurofibroma, intradermal naevus and haemangioma. Although clinical behaviour is benign, lesions may locally recur when incompletely removed (1188).

**Etiology**

Degeneration, ischemia (808) or the paracrine influence of mast cells (1842) may create the cytologic atypia of PF (1188).

**Histopathology**

PF are circumscribed, dome-shaped to polypoid, hypocellular dermal proliferations of spindle and irregularly shaped stellate or multinucleate cells. Lesional cells have scant cytoplasm and large, pleomorphic, hyperchromatic nuclei with small nucleoli and rare mitotic figures. Foam cells are rarely present. Haphazardly arranged, hyalinized dermal collagen is admixed with moderate mucin. The collagenous bundles in pleomorphic sclerotic fibromas are more storiform and clefted (458,808,1523). Myxoid (1614) and sclerotic variants have been described (808,1523).

**Immunoprofile**

Lesional cells are positive for muscle specific actin, CD34 and rarely alpha-1 antichymotrypsin (1188,1988).

**Differential diagnosis**

The histologic differential diagnosis includes: atypical fibroxanthoma, variants of dermatofibroma, fibrosarcoma, fibrous papule of the face, angiofibroma, giant cell fibroblastoma, desmoplastic Spitz naevus and fibroepithelial polyp with monster cells (1188).

**Giant cell fibroblastoma**

**Definition**

Giant cell fibroblastoma (GCF) is a histologic variant of DFSP, which primarily affects children.

**ICD-O code**

8834/1

**Epidemiology**

GCF is a rare tumour that primarily affects children in the first decade of life, with a strong male predilection. Occasional cases have also been reported in adults (751).

**Localization**

GCF most commonly affects the trunk, shoulder region and groin (similar to DFSP), but other reported sites include the extremities and head and neck (971,2174,2338).

**Clinical features**

Giant cell fibroblastoma is described as a slow growing, firm, dermal or subcutaneous mass which is painless and asymptomatic.
Macroscopy
Grossly, GCF is a firm yellow or grey tumour with gelatinous or rubbery consistency and without haemorrhage or necrosis (751,2174).

Histopathology
GCF is usually a subcutaneous tumour, but it often extends into the overlying dermis. Cellularity is variable, but for the most part, GCF is a hypocellular neoplasm composed of wavy spindle shaped cells and scattered giant cells set within a stroma that varies from myxoid to collagenous to sclerotic and contains scattered mast cells. Scattered giant cells with hyperchromatic and angulated nuclei are characteristic. Most giant cells are multinucleated, but some are mononucleated. The nuclei of multinucleate cells are either conglomerated towards the centre of the cell or arranged peripherally, in a characteristic floret pattern. Irregularly branching “angiectoid” spaces which resemble the vascular spaces of lymphangiomata are characteristic but are not seen in all cases. These are lined by spindle and multinucleate cells with morphology identical to those seen in the surrounding stroma. Cellular areas representing DFSP or less often pigmented DFSP (Bednar tumour) may be present. Recurrent lesions are uncommon, but when they occur, the lesions may show a pattern of DFSP. Fibrosarcomatous transformation of GCF has been reported in a recurrent lesion originally diagnosed as DFSP (1841).

Immunoprofile
The stromal and lining cells are CD34 positive, but negative for VWF (VIIIrAg), CD31, S100, actin, desmin, and EMA (971,2338).

Differential diagnosis
Since CD34 can be focally positive in other soft tissue lesions, finding the characteristic giant cells is important in diagnosing GCF.

Histogenesis
GCF and DFSP are currently classified as neoplasms derived from fibroblasts, but CD34 positivity suggests possible derivation from interstitial dendritic cells (971).

Somatic genetics
Both GCF and DFSP exhibit an identical t(17;22) (q22;q13) translocation, which in some cases results in a ring chromosome. The t(17;22) translocation fuses the collagen type I alpha 1 gene from chromosome 17q22 to the platelet-derived growth factor β chain gene from chromosome 22q13, resulting in a chimeric COL1A1-PDGFB gene that encodes for a transforming protein with biologic effects similar to normal PDGFB. The neoplastic cells not only harbour the mutation, but also have PDGFB receptors on their cell surface, resulting in an autocrine loop whereby the tumour cells stimulate their own growth (1735).

Prognosis and predictive factors
Like DFSP, GCF is a locally aggressive tumour of intermediate malignancy, with up to 50% local recurrence in the original series. Metastases from GCF have not been reported.

Dermatofibrosarcoma protuberans

Definition
Dermatofibrosarcoma protuberans (DFSP) is a mesenchymal neoplasm of the dermis and subcutis, generally regarded as a superficial low-grade sarcoma (1605,2491).

ICD-O code
8832/3

Synonym
Progressive and recurring dermatofibroma.

Epidemiology
DFSP typically presents during early or middle adult life, with male predominance. However, there is evidence that many tumours may have begun during childhood and become apparent during young adulthood.

Localization
The tumour occurs most commonly on the trunk, including chest, back, and abdominal wall. Less commonly, the neoplasm is located on the proximal extremities; it rarely involves the distal extremities. The head and neck, especially the scalp, are also commonly involved. The vulva (1377) and parotid gland are unusual sites of involvement.

Prognosis and predictive factors
Like DFSP, GCF is a locally aggressive tumour of intermediate malignancy, with up to 50% local recurrence in the original series. Metastases from GCF have not been reported.
Soft tissue tumours

times be observed as plaque-like areas of induration, often with peripheral red or blue discolouration. These tumours may resemble morphoea (localized scleroderma) or a morphoeic basal cell carcinoma. The lesion expands slowly, and eventuates in the typical, fully developed protuberant appearance with single or multiple nodules on a plaque-like base. Fungating ulcerated lesions with satellite nodules characterize an advanced neoplasm.

Patients with advanced DFSPs do not exhibit signs and symptoms of chronic wasting, as seen in patients with aggressive, high-grade soft tissue sarcomas. Previous burns, surgical scars, and antecedent trauma have been reported in association with this tumour. There are reports of DFSP occurring at Bacille-Calmette-Guérin (BCG) vaccination sites (1558), and in association with chronic arsenism (2176), acanthosis nigricans, and acrodermatitis enteropathica (2161). The tumour may show rapid enlargement during pregnancy (2329).

Macroscopy
Most excised primary DFSPs are indurated plaques with one or more associated nodules. Multiple discrete, protuberant skin and subcutaneous tumours are more characteristic of recurrent neoplasms. Often, there is evidence of a surgical scar on the skin surface of the tumourous tissue. Ulceration may be present. The cut surface of the tumour is grey-white and firm, with occasional areas showing a gelatinous or translucent appearance, corresponding to microscopic areas of myxoid change. Haemorrhage and cystic change are sometimes seen. However, necrosis, a common feature of malignant fibrous histiocytoma, is rarely observed in DFSP. It is unusual to encounter DFSP confined solely to subcutaneous tissue without involvement of the dermis (629).

Histopathology
DFSP diffusely infiltrates the dermis, and invades into subcutaneous tissue, especially along the fibrous septa of fat. The epidermis is usually uninvolved. A grenz zone may be present. In a well-sampled specimen, the tumour shows some variation in histologic features. The centre of the tumour is typically composed of compact, uniform, slender, mildly atypical, spindle-shaped cells, arranged in a whorled, storiform, or cartwheel pattern. The tumour cells tightly encase skin appendages without destroying them. Nuclear pleomorphism is inconspicuous, and mitotic activity is low-to-moderate (<less than 5/10 HPF). Some tumours have a prominent myxoid matrix, and microscopic myxoid changes have been observed in both primary and recurrent tumours (368). Superficial areas of the neoplasm are less cellular, and spindle cells are separated by dermal collagen. The deep portion of the tumour shows a proliferation of spindle cells which expand fibrous septa and interdigitate with fat lobules, resulting in a honeycomb appearance. In some tumours, giant cells similar to those of giant cell fibroblastoma are seen. At times, peculiar myoid nodules may be present, which represent a nonneoplastic myointimal or myofibroblastic proliferation. Occasional foci may resemble a low-grade fibrosarcoma, with longitudinal fascicles of spindle cells demonstrating more prominent nuclear atypia and mitotic activity (but not greater than 5/10 HPF). Such areas have been seen in a minority of primary or recurrent lesions (853).

Immunoprofile
DFSP cells label diffusely and strongly with antibodies to CD34 and vimentin. CD34 positivity may be lost in nodular areas showing a gelatinous or translucent appearance, corresponding to microscopic areas of myxoid change. Haemorrhage and cystic change are sometimes seen. However, necrosis, a common feature of malignant fibrous histiocytoma, is rarely observed in DFSP. It is unusual to encounter DFSP confined solely to subcutaneous tissue without involvement of the dermis (629).

Differential diagnosis
Benign and cellular fibrous histiocytoma or dermatofibroma (DF) can be differentiated from DFSP by the presence of epidermal (sometimes basal cell) hyperplasia, more prominent collagenous stroma, collagen trapping, and infiltration of the fibrous septa, but minimal extension into fat lobules. Immunostains are also helpful. DF contains a focally but not diffusely positive CD34 spindle cell component. P75 and stromelysin 3 are negative, and tenasin is positive at the dermoeipidermal zone (DEZ) in DFSP (1180). Stromelysin 3 is not expressed in the cells of a DFSP in contrast to dermatofibroma in which it is invariably expressed (558).
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than DFSP. Necrosis is usually not a feature of DFSP, but is generally seen in MFH. Myxoid liposarcoma is distinguished from myxoid forms of DFSP by the presence of lipoblasts, negative CD34 staining, and deep soft tissue involvement.

Histogenesis

DFSP and its variant, giant cell fibroblastoma (GCF) are currently classified as neoplasms derived from fibroblasts. CD34 labelling suggests a close linkage to dermal dendrocytes.

Somatic genetics

DFSP and GCF exhibit an identical chromosomal translocation. See page 259.

Prognosis and predictive factors

As with GCF, DFSP has a significant risk of local recurrence. The average recurrence rate in reported cases treated by wide local excision (2-3 cm.) is 18%. A much higher recurrence rate (43%) is reported in tumours treated by superficial or incomplete excisions only (853)

Local recurrence usually develops within three years after initial surgery. Metastasis occurs rarely.

Dermatofibroma (fibrous histiocytoma)

Definition

Dermatofibroma (fibrous histiocytoma) (21) is an ill-defined, predominantly dermal lesion characterized by a variable number of spindle and/or rounded cells. A variable admixture of inflammatory cells, coarse collagen bundles in haphazard array, and variable epidermal, melanocytic and folliculo-sebaceous hyperplasia are present.

ICD-O code

8832/0

Synonyms

Histiocytoma (cutis) (2134), fibroma durum, subepidermal nodular fibrosis or sclerosis (1602), sclerotic or sclerosing fibroma (1895), sclerosing haemangioma (910).

Epidemiology

Dermatofibroma is a very common lesion and may develop at any age, but particularly during the third and fourth decades. The gender distribution varies among different populations.

Etiology

The etiology has not been established unequivocally. It is controversial whether it is an inflammatory (21,2590,2591) or neoplastic process (365,518,522,919). Dermatofibroma has been reported following local injuries such as trauma, insect bites or folliculitis, suggesting an inflammatory etiology. By contrast some examples have been reported to be clonal, supportive of a neoplastic etiology (457,1078,2422).

Localization

Most lesions, including various clinicopathological variants, occur on the extremities (840,1081,1114,1155,1187, 1346,1786,1895,2115,2587,2592-2594) and trunk (187,370,2403). Rare cases occur on the face (1583).

Clinical features

Most lesions are single, round, oval to targetoid papules. Early lesions are reddish, but older ones are brown to skin coloured, frequently with a brown rim at the periphery. They usually evolve rapidly. Dermatofibromas are moderately well circumscribed; the consistency usually is hard, but may be cystic, eroded or crusted when secondary changes such as prominent haemorrhage, lipidization or trauma alter the lesions. Most lesions are flat, slightly elevated or show a shallow dell. The “dimpling” sign, when lesions are squeezed between the thumb and index finger, is characteristic. Occasionally, there may be a few, up to several dozen, sometimes grouped (“agminated”) papules. Multiple dermatofibromas are regarded as a marker of immune suppression; they have been observed in Black females with systemic lupus erythematosus; various other autoimmune disease such as Sjögren syndrome, pemphigus vulgaris, myasthenia gravis and ulcerative colitis treated with immunosuppressive drugs; occasionally in renal graft recipients or AIDS patients. Still other lesions form plaques or tumours. Dermatofibromas usually are long standing lesions which cause no symptoms.

Macroscopy

Gross examination reveals a moderately well-circumscribed, hard papule, nodule or tumour. The cut surface reveals a skin-coloured to distinctive yellow colour, which may show areas of haemorrhage and lipidization and then become cystic.
Histopathology
Dermatofibromas show a dense infiltrate of spindle-shaped and/or round cells, some of which may be fibrocytes and/or macrophages, centred in the reticular dermis and sometimes, the upper part of the subcutis. Early lesions are rich in macrophages, some of which may be siderophages, and/or lipophages, others multinucleate, e.g. Touton or foreign body giant cells. Established lesions show prominent cellularity and coarse haphazardly arranged collagen bundles. They are frequently arranged in short fascicles that interweave (“storiform”), sometimes with a sclerotic centre. Lesions are ill-defined and at the periphery there can be collagen trapping by lesional cells (“collagen ball formation”). Epidermal, melanocytic and folliculosebaceous hyperplasia is characteristically found above the lesions, and this can be so prominent that buds of hair follicles mimic superficial basal cell carcinoma. Rare cases show smooth muscle proliferation (1381). Lymphocytes are often spread throughout the lesion with frequent prominence at the periphery, but may be lacking in later stages. At times foam cells may be prominent in deeper areas adjacent to subcutaneous fat. A wide number of variants of dermatofibromas have been proposed (369). Early lesions may show prominent proliferation of blood vessels, previously called sclerosing haemangioma (910), more recently haemangiopericytoma-like fibrous histiocytoma (2594). Prominent lipophages and siderophages are seen in the xanthomatous/histiocytic variant (1081,1114) and haemosiderorrhagic variant (2036), respectively. Older lesions become progressively fibrotic, with shrinkage of the lesion, particularly seen in atrophic dermatofibroma. Other variants show a heavy eosinophilic infiltrate {40} or pseudolymphomatous features (150), respectively. Lichenoid, erosive and ulcerated variants (2034) have also been reported. Deep penetrating variants extend into the subcutis and may be easily confused with dermatofibrosarcoma protubersans (1187,2587). Other rare variants include dermatofibroma with monster cells (2316); ossifying dermatofibroma with osteoclast-like giant cells (1345); granular (2403) and clear cell dermatofibromas {1786,2592}; myxofibroblastic dermatofibroma with slender cytoplasmic cell extensions (2593); myxoid dermatofibromas {2183,2588}; or combined dermatofibromas (2589), which show a combination of several unusual histopathologic features in one lesion.

Immunoprofile
Dermatofibromas reveal a variable immunohistochemical profile: early lesions are rich in reactivity for macrophage markers such as PGM1 or KP1 (CD68), but also exhibit strong reactivity for factor XIIIa in both macrophages and fibroblasts (2590). This reactivity is mostly seen at the periphery and continuously diminishes with the ageing of the lesion to be completely absent in atrophic variants. Actin expression is variably seen in dermatofibromas particularly in the myofibroblastic variant (2593). Occasionally dermatofibromas are focally positive for CD34 (1840,2584). Recently, 3 expression has been reported. It is not expressed in DFSP (558).

Differential diagnosis
The most important histologic differential diagnoses are dermatofibrosarcoma protuberans (particularly with the cellular variant of dermatofibroma) and Kaposi sarcoma. Dermatofibrosarcoma protuberans is poorly circumscribed, usually much broader and deeper with irregular dissection of subcutis, and shows cells with wavy nuclei in association with delicate fibrillary bundles of collagen frequently arranged in a storiform pattern. In contrast to dermatofibroma it is regularly positive for CD34. Kaposi sarcoma in nodular and tumour stage is characterized by erythrocytes extravasated into slits between interweaving fascicles of spindle-shaped cells; often, tiny pink hyaline globules that represent degenerated erythrocytes are found in these spindle-shaped endothelial cells. Lesions are positive for CD34 and vascular markers such as CD31.

Variants
**Aneurysmal fibrous histiocytoma**
This is not uncommon (367,2054). It may rapidly enlarge because of spontaneous or traumatic haemorrhage into a previously unspectacular lesion or rarely de novo development, and frequently is painful. Clinically, it may mimic nodular melanoma or nodular Kaposi sarcoma. Histology reveals extravasation of erythrocytes, pseudovascular spaces and iron deposits. This histology may occasionally also be confused with melanoma or nodular Kaposi sarcoma, yet the absence of melanocytic as well as vascular markers in the spindle cells easily excludes these simulants.

**Epithelioid cell histiocytoma**
This lesion (840,1155), including a cellular variant (794) is rare. It occurs on the upper extremities and trunk as a skin-coloured to reddish-brown, hard, exophytic papule, frequently thought to be a Spitz naevus. Histology reveals a lesion mostly restricted to the papillary dermis, prominent epidermal hyperplasia (“col- larette”) and a sheet-like infiltrate of epithelioid to scolloped fibroblasts. These features may also closely simulate Spitz naevus, yet lesions are negative for melanocytic markers, but positive for factor XIIIa.

**Cellular fibrous histiocytoma**
This variant is rare (370). It occurs on the trunk or distal extremities and has a tendency to recur when incompletely excised. Histology reveals a dense, frequently deeply infiltrating lesion of spindle cells in an otherwise typical dermatofibroma. There may be moderate nuclear atypia, occasional mitoses and bizarre giant cells and these lesions have therefore also been called pseudosarcomatous or atypical fibrous histiocytomas (794). Exceptional cases of this variant have been reported to metastasize and, accordingly, they should always be completely excised.

Prognosis and predictive factors
The vast majority of lesions are benign. Occasionally incomplete excision may result in recurrence. The cellular and aneurysmal variants and lesions of the face may recur in a significant percentage of cases (1583). Exceedingly rare cases of local aggressive growth or metastases to local or regional lymph nodes or even with wide spread metas tases to lung have been recorded in the cellular variant.