The background of the page is a microscopic image of tissue, likely stained with hematoxylin and eosin (H&E). The tissue shows various cellular structures, including what appears to be a large vessel or duct structure on the right side, characterized by a thick, reddish-stained wall and a central lumen. The surrounding tissue consists of numerous cells with pink cytoplasm and purple nuclei. A semi-transparent white box is centered on the page, containing text.

CHAPTER 7

Vascular Tumours

Benign vascular tumours are very common and most frequently occur in the skin (see WHO classification of skin tumours). At all sites, it is often difficult to determine whether benign vascular lesions are malformations, true neoplasms or, in some cases, reactive processes. Similarly, it remains essentially impossible to reliably distinguish blood vessel endothelium from lymphatic endothelium, which probably reflects the close functional and embryogenetic relationship between these cell types.

Changes and advances since the 1994 WHO classification include the characterization of various newly recognized entities, particularly in the categories of intermediate malignancy, including the kaposiform, retiform and composite types of haemangioendothelioma. Use of the term 'haemangioendothelioma' remains problematic since, in the past, this term has been used variably for benign, intermediate and malignant lesions. In current practice, the term usually connotes intermediate malignancy, except in the context of epithelioid haemangioendothelioma, the metastatic rate of which is high enough (albeit much lower than conventional angiosarcoma) to justify its classification as malignant.

Angiosarcomas in soft tissue are now more frequently recognized, in large part to the realization that many such tumours have epithelioid cytomorphology at deep soft tissue locations, including the pleural and peritoneal cavities.

Haemangiomas

E. Calonje

Synovial haemangioma

Definition

Synovial haemangioma (SH) is a benign proliferation of blood vessels arising in a synovium-lined surface, including the intra-articular space and bursa. Similar lesions occurring within the tendon sheath do not fall into this diagnostic category.

Epidemiology

SH is very rare. Most patients are children or adolescents and there is a predilection for males {509}.

Sites of involvement

The most common site by far is the knee, followed much less commonly by the elbow and hand.

Clinical features

The tumour presents as a slowly growing lesion often associated with swelling and

joint effusion {509}. Recurrent pain is a frequent symptom. In about one third of cases pain is not a feature. Magnetic resonance imaging is the best radiological technique to identify the lesion particularly with regards to the extent of involvement {835}.

Aetiology

The presentation of most lesions at a young age suggests that SH is a form of vascular malformation. Trauma is unlikely to be of relevance in the pathogenesis.

Macroscopy

Numerous congested, variably dilated vessels of different calibre can be seen and the tumour can be fairly circumscribed or diffuse.

Histopathology

The tumour often has the appearance of a cavernous haemangioma with multiple dilated thin-walled vascular channels. A smaller percentage of cases have the appearance of either a capillary or arteriovenous haemangioma. The vascular channels are located underneath the synovial membrane and are surrounded by myxoid or fibrotic stroma. Haemosiderin deposition can be prominent. Secondary villous hyperplasia of the synovium is present in some cases.

Prognostic factors

Small lesions are usually easy to remove completely with no risk of local recurrence. When more diffuse involvement of the joint is present, complete excision can be difficult to achieve.

Intramuscular angioma

Definition

Intramuscular angioma (IA) is defined as a proliferation of benign vascular channels within skeletal muscle and it is associated in most instances with variable amounts of mature adipose tissue.

ICD-O code 9132/0

Synonyms

Intramuscular haemangioma, intramuscular angioliipoma.

Epidemiology

Although relatively uncommon, IA is one of the most frequent deep-seated soft tissue tumours. The age range is wide but adolescents and young adults are most commonly affected (in up to 90% of cases) {44,152,651}. Lesions have often been present for many years and it is therefore likely that many examples are congenital. There is an equal sex incidence.

Sites of involvement

IA most commonly affects the lower limb, particularly the thigh, followed by the head and neck, upper limb and trunk. Rare cases can present in the mediastinum and retroperitoneum.

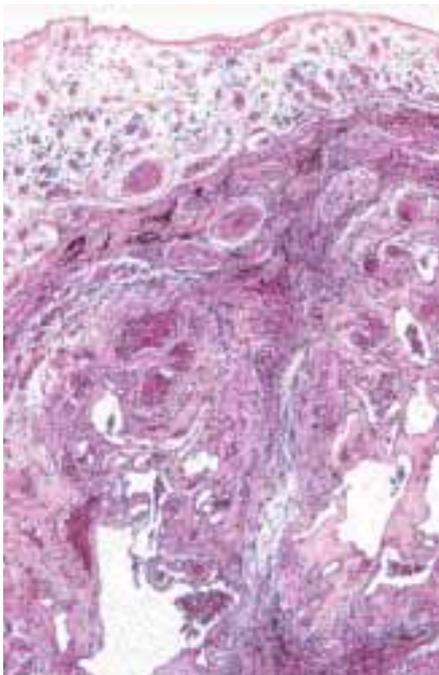


Fig. 7.01 Synovial haemangioma. A mixture of cavernous and capillary vascular channels underlie the synovium.

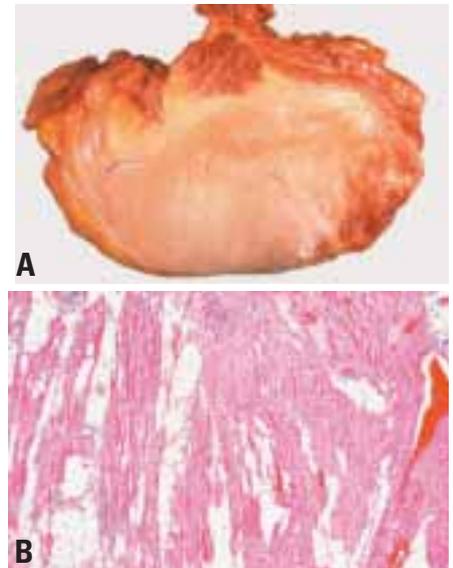


Fig. 7.02 Intramuscular haemangioma. **A** This lesion was excised from the rectus abdominis muscle of a young adult female. Note the poorly circumscribed margins and prominent fatty stroma. **B** Extensive replacement of the muscle by dilated vascular channels with focal thrombosis. Note the prominent adipocytic component.

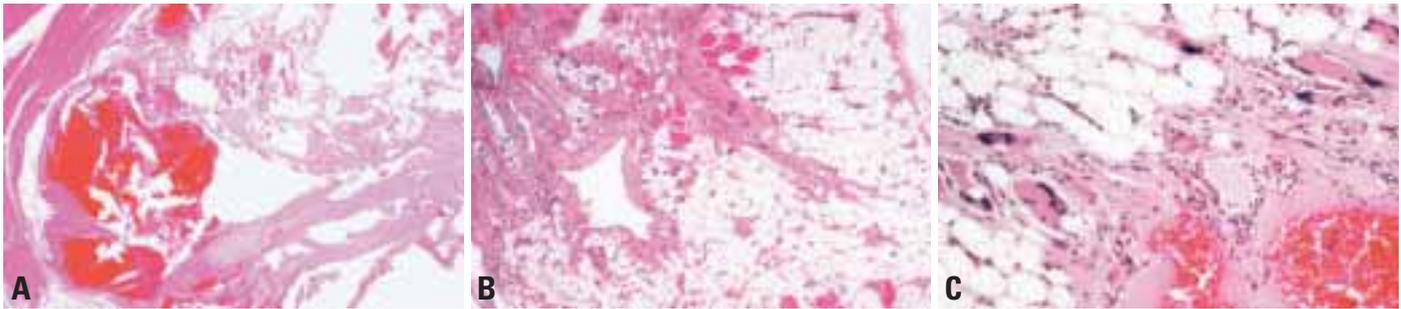


Fig. 7.03 Intramuscular haemangioma. **A** Predominance of cavernous-like vascular spaces. **B** Extensive adipocytic component with muscle atrophy. **C** Entrapped muscle fibres with hyperchromatic, reactive nuclei.

Clinical features

The typical presentation is that of a slowly growing mass which is often painful, particularly after exercise. Pain is mainly present in tumours located in the limbs. Radiological examination often reveals the presence of calcification secondary to phleboliths or metaplastic ossification.

Aetiology

It is likely that these lesions are malformations and there is no relation to trauma.

Macroscopy

Tumours are often large and there is diffuse infiltration of the involved muscle. Variably sized vascular channels with thrombosis and haemorrhage are usually readily seen. The appearance of the tumour can be solid and yellowish as a result of the presence of adipose tissue. Lesions also appear solid when capillaries predominate.

Histopathology

IA has been traditionally classified according to the vessel size into small (capillary), large (cavernous) and mixed. This is not practical, however, as most tumours contain a mixture of vascular channels frequently including lymphatics. IA usually consists of large thick-walled veins, a mixture of cavernous-like vascular spaces and capillaries or a prominent arteriovenous component. Tumours purely composed of capillaries have a predilection for the head and neck area and those with a predominant cavernous lymphatic component are seen mainly on the trunk, proximal upper limb and head. Variable amounts of mature adipose tissue are almost always present and may be very prominent. This explains why IA was sometimes known in the past as angiolipoma {1264}. Atrophy of muscle fibres secondary to the infiltra-

tive nature of the tumour often results in degenerative/reactive sarcolemmal changes with hyperchromatic nuclei.

Prognostic factors

The rate of local recurrence is high (between 30 to 50%) and therefore wide local excision is recommended.

Venous haemangioma

Definition

Venous haemangioma (VH) is composed of veins of variable size, often having thick muscular walls. Intramuscular angiomas and angiomatosis can be composed almost exclusively of veins but are usually intermixed with other vessel types. These subtypes are described under their respective headings.



Fig. 7.04 Venous haemangioma with typically numerous prominent thick-walled veins.

ICD-O code 9122/0

Epidemiology

Pure VHs are rare and mainly present in adults.

Sites of involvement

Tumours present in the subcutaneous or deeper soft tissues with predilection for the limbs.

Clinical features

VH often presents as a long-standing slowly growing tumour. Radiological examination often shows the presence of calcification due to phleboliths.

Aetiology

The clinical evolution and clinicopathological features suggest that these lesions represent vascular malformations.

Macroscopy

VH is ill defined and consists of dilated congested vascular spaces with areas of haemorrhage.

Histopathology

VH typically consists of large thick-walled vessels, which are variably dilated and commonly display thrombosis with occasional formation of phleboliths. Widely dilated vessels can show attenuation of their walls, mimicking a cavernous haemangioma.

Elastic stains reveal the absence of an internal elastic lamina. This aids in the distinction from an arteriovenous haemangioma.

Prognostic factors

Deep-seated tumours are difficult to excise and can recur locally but subcutaneous tumours do not show a tendency to recur.

Arteriovenous haemangioma

Definition

Arteriovenous haemangioma (AVH) is a non-neoplastic vascular lesion characterized by the presence of arteriovenous shunts. There are two distinctive variants {63,1825}: deep-seated and cutaneous (cirroid aneurysm or acral arteriovenous tumour; see WHO classification of skin tumours).

When these lesions involve multiple tissue planes, they are termed angiomatosis (see page 161). AVH should not be confused with juvenile, cutaneous (cellular) haemangiomas as they do not regress spontaneously.

ICD-O code 9123/0

Synonym

Arteriovenous malformation.

Epidemiology

Deep-seated AVH is uncommon and affects children and young adults.

Sites of involvement

AVH affects predominantly the head and neck followed by the limbs.

Clinical features

Angiography is an essential tool to confirm the diagnosis and establish the extent of the disease. Lesions are often associated with a variable degree of arteriovenous shunting and this can be severe enough to induce limb hypertrophy, heart failure, and consumption coagulopathy (Kasabach-Merritt syndrome). Pain is also a frequent symptom and superficial cutaneous changes mimicking Kaposi sarcoma clinically and histologically can be seen (pseudo-Kaposi sarcoma or acroangiokeratitis) {2046}. The presence of shunting can be confirmed clinically by auscultation.

Macroscopy

Tumours are ill defined and contain variable numbers of small and large blood vessels, many of which are dilated.

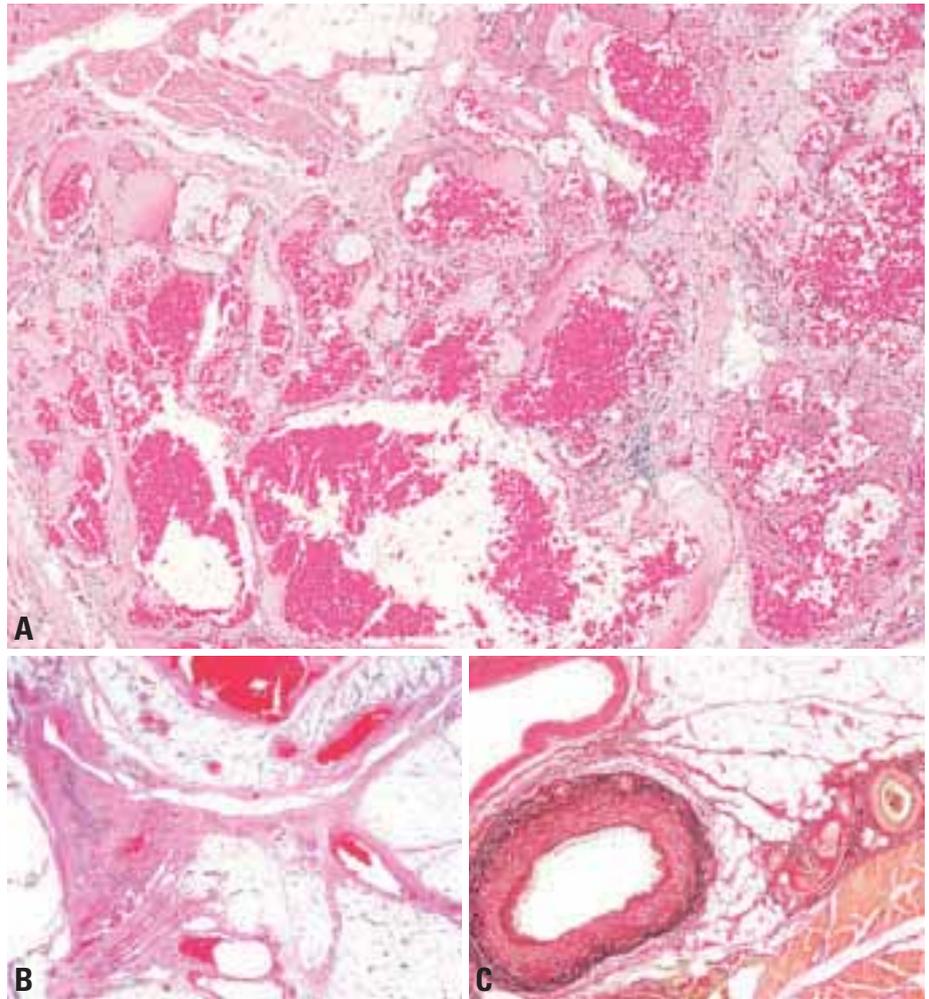


Fig. 7.05 Arteriovenous haemangioma. **A** In some cases, cavernous vascular spaces predominate. **B** Extensive infiltration of the subcutaneous tissue by large vessels. **C** An elastic stain is useful to determine the type of vessels (elastic van Gieson).

Histopathology

This diagnosis always requires clinicopathological and radiological correlation. AVH is characterized by large numbers of vessels of different size, which include veins and arteries with the former largely outnumbering the latter. Areas resembling a cavernous or capillary haemangioma are frequent, as are thrombosis and calcification. Recognition of arteriovenous shunts is difficult and requires examination of numerous serial sections. Fibrointimal thickening in veins is a useful

diagnostic clue.

Elastic stains are helpful in distinguishing between arteries and veins. Negative GLUT-1 staining may facilitate distinction from juvenile haemangioma {1582}.

Prognostic factors

Treatment is difficult because of the degree of involvement, which has to be determined by angiographic examination. Local recurrence is common because of the difficulties in achieving complete excision.

Epithelioid haemangioma

J.F. Fetsch

Definition

A benign vascular tumour with well formed but often immature vessels, the majority of which are lined by plump, epithelioid (histiocytoid) endothelial cells with amphophilic or eosinophilic cytoplasm and a large nucleus with an open chromatin pattern and central nucleolus. Subcutaneous examples are usually associated with a muscular artery. Most cases have a prominent inflammatory component.

ICD-O code 9125/0

Synonyms

Angiolymphoid hyperplasia with eosinophilia {314, 661, 1059, 1384, 1612, 1805, 2248}, nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis {158}, subcutaneous angioblastic lymphoid hyperplasia with eosinophilia {1769} and inflammatory angiomatoid nodule.

Epidemiology

Epithelioid haemangioma affects a wide age range, peaking in the third through fifth decades {661, 1612}. Females appear to be affected more commonly than males.

Sites of involvement

The most frequently affected sites are the head, especially the forehead, preauricular area, and scalp (often in the distribution of the superficial temporal artery), and the distal portions of the extremities, especially the digits {661, 1612}.

Clinical features

The majority of patients present with a mass of a year or less in duration. However, some examples have been reported to be present for as many as 15 years before excision {661, 1612}. The process is usually uninodular, but multinodularity (generally in contiguous areas) is encountered with some frequency. Most examples affect

the subcutis, with dermal examples being less frequent, and deep-seated cases being rare {661, 1612}. Rare cases arise from a large vessel. The most frequent preoperative clinical impressions are an epidermal cyst or angioma {1612}.

Aetiology

There remains considerable controversy as to whether epithelioid haemangioma (angiolymphoid hyperplasia with eosinophilia) is a reactive lesion or a true neoplasm. Features that lend support for a reactive process include: 1) a predilection for superficial soft tissue sites that overlie bone and have minimal soft tissue padding, coupled with a compelling history of trauma in up to 10% of cases {661, 1612}, 2) a tendency for subcutaneous examples to be well delineated and symmetrically organized around a larger vessel that may have evidence of damage (e.g., fibrointimal proliferation, a disrupted elastic lamina, or mural disruption), 3) a pronounced inflammatory reaction, and 4) some morphologic evidence supporting lesional maturation over time. However, the alternative view that this is a true benign neoplasm with self-limiting biologic potential cannot be dismissed, especially in view of the local recurrence rate.

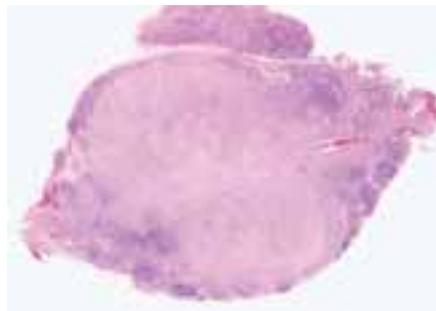


Fig. 7.06 Subcutaneous epithelioid haemangioma, showing circumscription, a peripheral lymphoid reaction, and symmetrical growth around a muscular artery.

Macroscopy

These lesions are usually 0.5–2.0 cm in size, with rare examples exceeding 5 cm {1612}. Apart from size, the gross characteristics of this process are not well-described. Many examples may have a rather nonspecific nodular appearance. Some examples with retained blood may have an appearance suggestive of a haemangioma. Occasionally, subcutaneous examples may resemble a lymph node because of circumscription and a peripheral lymphoid reaction.

Histopathology

Subcutaneous examples of epithelioid haemangioma are characterized by a prominent proliferation of small, capillary-sized vessels lined by plump, epithelioid endothelial cells. The vessels typically have an immature appearance and they may lack a well defined lumen, but they are well formed with single cell layering of the endothelium and an intact myopericytic/smooth muscle layer. The endothelial cells have amphophilic or eosinophilic cytoplasm that is sometimes vacuolated, and they contain a single, relatively large, nucleus with an open chromatin pattern, and often, a central nucleolus. The process is usually well demarcated from the surrounding soft tissue, and commonly, it is associated with (sometimes centred around) a larger vessel, usually a muscular artery. An inflammatory milieu rich in eosinophils and lymphocytes is present in the overwhelming majority of cases, and many examples are bordered by a prominent lymphoid reaction with follicle formation. It is common to encounter epithelioid endothelial cells within the lumen of the larger vessel, either replacing part of the normal endothelial lining or "coating" fibrin fronds, as seen in papillary endothelial hyperplasia. Cross-sections of the larger vessel may also reveal epithelioid

endothelial-lined channels that transgress the vessel wall and communicate with the surrounding vascular proliferation.

Dermal examples of epithelioid haemangioma also feature a proliferation of small vessels, lined by epithelioid endothelial cells, set in an inflammatory milieu rich in lymphocytes and eosinophils. However, in this location,

the vessels often have a more mature appearance with a well canalized lumen, and the endothelial cells are somewhat less plump, frequently more cobblestone or hobnail-like in appearance. Also, dermal examples are less circumscribed and often lack lymphoid follicles. Finally, these superficial lesions are not usually associated with a larger central vein or muscular artery.

Immunophenotype

The epithelioid endothelial cells of epithelioid haemangioma are immunoreactive for CD31 and factor VIIIrAg. Immunoreactivity for CD34 is also present, though often to a lesser degree. Infrequently, limited keratin expression may be detected. Immunostaining for alpha-smooth muscle actin or musclespecific actin is helpful in demonstrating an intact myopericytic layer around the immature vessels. Actin-positive myopericytes are generally present to a much lesser extent in malignant vascular tumours such as epithelioid haemangioma and epithelioid angiosarcoma.

Prognostic factors

Complete local excision and follow-up are optimal management for epithelioid haemangioma. Local recurrence is reported to occur in up to one-third of patients [1612]. Whether this is due to persistence of an underlying vascular anomaly (e.g., an arteriovenous shunt) that incites regrowth or an indication of true neoplastic potential is unresolved. Metastases do not occur. There is one report of apparent regional lymph node seeding that had no adverse affect on patient outcome with 5 years follow-up [1769].

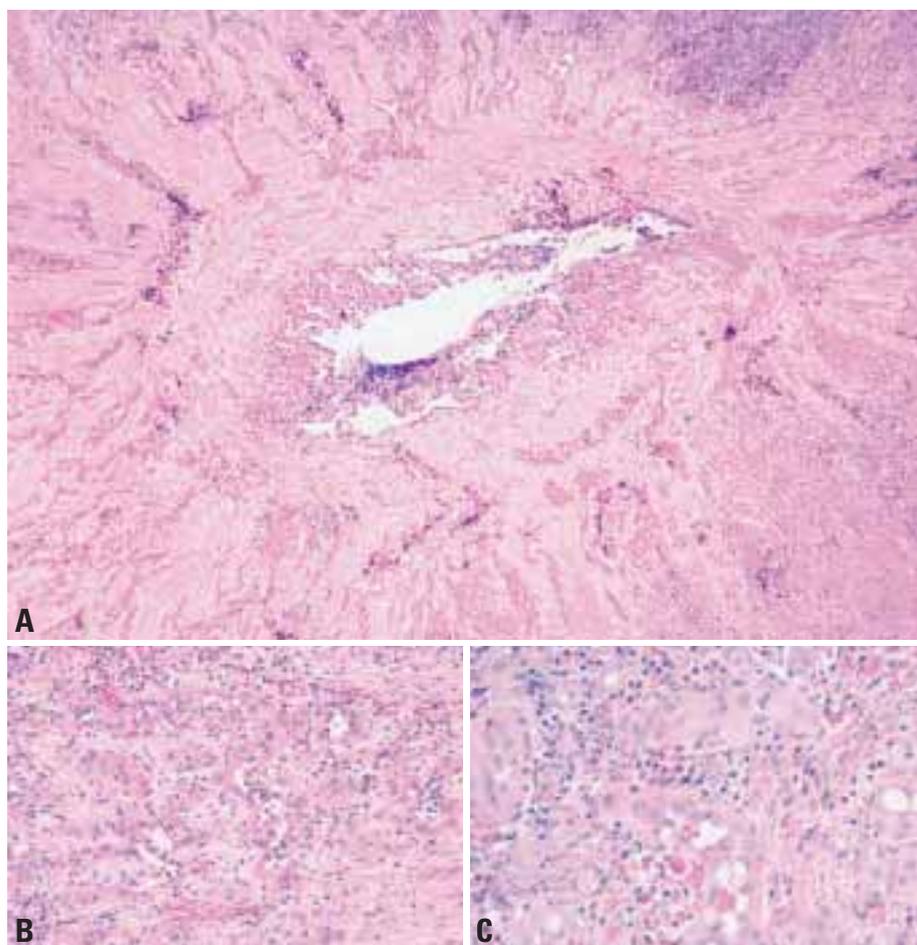


Fig. 7.07 Epithelioid haemangioma. **A** Involvement of a muscular artery. Note the presence of an intraluminal component, and the immature, but well formed, vessels around the artery. **B,C** Immature vessels, lined by epithelioid endothelial cells. Note the presence of an inflammatory infiltrate rich in lymphocytes and eosinophils.

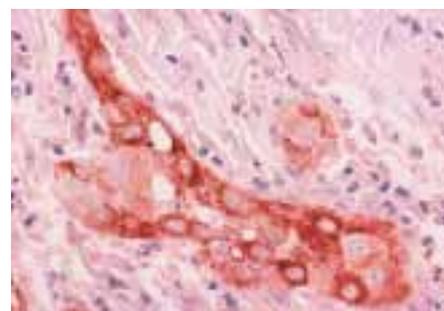


Fig. 7.08 Epithelioid haemangioma. The epithelioid endothelial cells are strongly reactive for factor VIIIrAg.

Angiomatosis

S.W. Weiss

Definition

Angiomatosis is a diffuse form of haemangioma that affects a large segment of the body in a contiguous fashion, either by vertical extension, to involve multiple tissue planes (e.g. skin, subcutis, muscle, bone), or by crossing muscle compartments to involve similar tissue types (e.g. multiple muscles). This definition implies that the diagnosis is a combined clinical and pathological one.

Synonyms and historical annotation

Vascular malformation, arteriovenous malformation, and venous malformation have been employed as synonyms for angiomatosis. These earlier terms underscore the prevailing view that angiomatosis probably represents congenital malformations (rather than neoplasms) which make their appearance during childhood. The term "infiltrating angiolipoma"; used to refer to intramuscular lesions composed of both a mature vascular and fatty component, has also been used for angiomatosis.

Epidemiology

Approximately two-thirds of cases develop within the first two decades of life and nearly all are apparent by age 40 years.

Females are affected with slightly greater frequency than males {1758}.

Sites of involvement

Over one half of cases occur in the lower extremities, followed by the chest wall, abdomen, and upper extremity.

Clinical features

Patients present with diffuse persistent swelling of the affected part, which occasionally waxes and wanes in size and is affected by strenuous activity. Only rarely is significant arteriovenous shunting leading to gigantism observed. Plain films of the affected region show an ill defined mass which on CT scan can sometimes be identified as vascular due to the presence of serpiginous densities corresponding to tortuous veins.

Macroscopy / Histopathology

The lesions are ill defined masses which vary from a few centimeters to 10-20 cm. in diameter. Although they vary in colour, many may have a fatty appearance, due to the presence of mature adipose tissue. Angiomatosis may assume one of two patterns. The more common pattern is that of a melange of venous, cavernous and capillary-sized vessels scat-

tered haphazardly throughout soft tissue. The venous vessels contain irregularly attenuated walls from which clusters of smaller vessels herniate in bouquet-like arrangement. In the second pattern the lesion resembles an infiltrating capillary haemangioma. Large amounts of mature fat frequently accompany both types. Although the first pattern is highly characteristic of angiomatosis, the diagnosis should not be made on this pattern alone, but on the combination of these changes in association with the clinical features {2240}.

Rare lesions with prominent glomus cells are classified as glomangiomas (see page 136).

Clinical behaviour

Although angiomatosis is considered a benign lesion, nearly 90% of cases persist (often mistakenly interpreted as true local recurrence). In some studies nearly 50% of patients develop multiple recurrences. Metastasis or malignant transformation has not been reported {510,978,1758}.

These recurrence rates probably reflect incomplete excisions in the face of extensive disease.

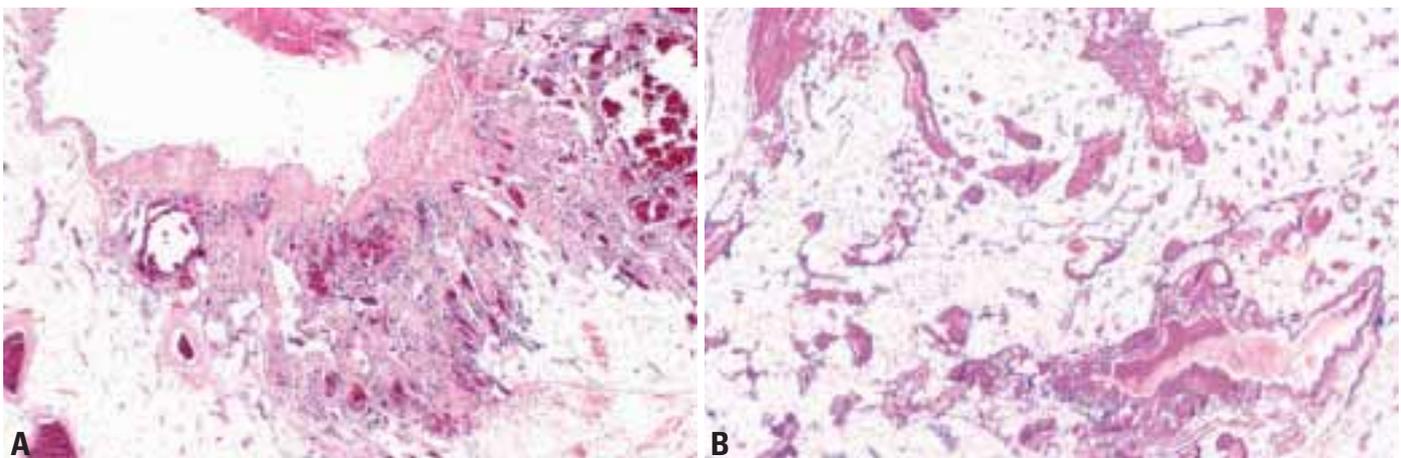


Fig. 7.09 Angiomatosis showing (A) clusters of small vessels radiating from a vein. B 1436 Note the diffuse growth pattern.

Lymphangioma

A. Beham

Definition

A benign, cavernous / cystic vascular lesion composed of dilated lymphatic channels. Lymphangioma circumscriptum and progressive lymphangioma are described in the WHO classification of skin tumours.

ICD-O code 9170/0

Synonym Cystic hygroma.

Epidemiology

Lymphangiomas are common paediatric lesions, which most often present at birth or during first years of life {47,375,671, 1045}. Some cases may be identified in Turner syndrome (and other malformative syndromes) and may be found in abortuses {375}. Cavernous/cystic lymphangioma of head and neck represents the most frequent subtype.

Sites of involvement

Cystic lymphangiomas are mostly located in the neck, axilla and groin, whereas the cavernous type occurs additionally in the oral cavity, upper trunk, limbs and abdominal sites including mesentery and retroperitoneum {47}.

Clinical features

The lesions present as rather circumscribed painless swellings, which are

soft and fluctuant at palpation, and can show displacement of surrounding organs at mediastinal or intraabdominal sites. Imaging procedures like ultrasonography display their cystic nature, angiography shows poor vascularization and CT scan reveals multiple, homogeneous, nonenhancing areas.

Aetiology

Early or even congenital appearance in life and lesional architecture are in favour of developmental malformations, with genetic abnormalities playing an additional role.

Macroscopy

Cavernous / cystic lymphangiomas correspond to a multicystic or spongy mass, the cavities of which contain watery to milky fluid.

Histopathology

Cavernous/cystic lymphangiomas are characterized by thin-walled, dilated lymphatic vessels of different size, which are lined by a flattened endothelium and frequently surrounded by lymphocytic aggregates. The lumina may be either empty or contain proteinaceous fluid, lymphocytes and sometimes erythrocytes. Larger vessels can be invested by a smooth muscle layer, and long-standing lesions reveal interstitial

fibrosis and stromal inflammation. Stromal mast cells are common and haemosiderin deposition is frequently seen.

Immunophenotype

The endothelium demonstrates variable expression of FVIII-rAg, CD31 and CD34 {704}.

Ultrastructure

The endothelium of thin-walled vessels is not enveloped by a basement membrane and no pericytes are attached to it, thus directly contacting with the interstitium. With increasing caliber the vessels may acquire pericytes and smooth muscle cells, respectively.

Genetics

Cystic lymphangiomas ("cystic hygroma") of the neck are often associated with Turner syndrome {289,339}.

Prognostic factors

Recurrences are due to incomplete surgical removal, whereas malignant transformation does not occur. Lymphangiomas of the neck/axilla sometimes extend to the mediastinum and may be of vital significance by compromising trachea, esophagus etc. Abdominal lesions can lead to intestinal obstruction.



Fig. 7.10 **A** Cystic lymphangioma, collapsed. The adjacent tube shows the milky lymph removed from the lesion. **B** Cystic lymphangioma in the lower neck of a fetus with Turner syndrome. **C** Large, partly cystic lymphangioma from mesentery and partially covered by adipose tissue.

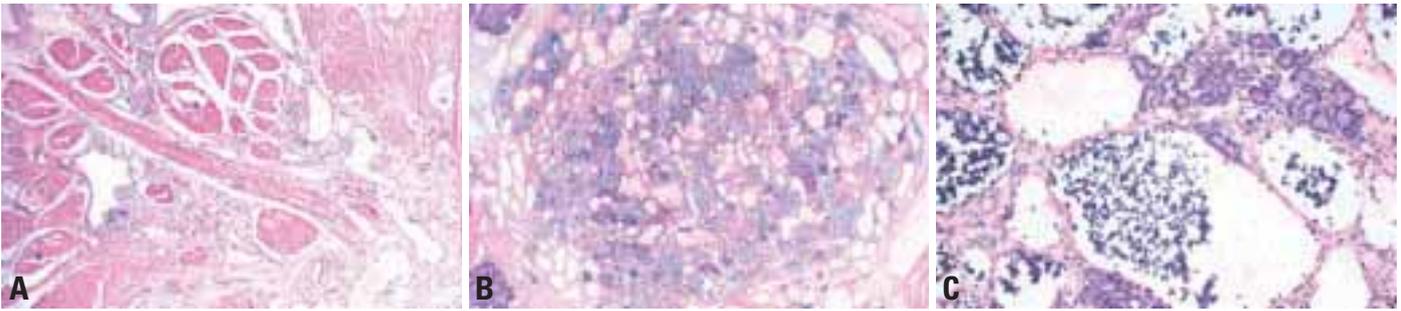


Fig. 7.11 Lymphangioma. **A** Multiple, cystic or ectatic, thin-walled lymphatic spaces infiltrating skeletal muscle. **B** Cystic, dilated lymphatic spaces with accompanying stromal lymphocytic aggregates, infiltrating the parotid gland in a sieve-like manner. **C** Thin-walled spaces of varying diameter, containing lymph and / or lymphocytes, and lined by flattened endothelium.

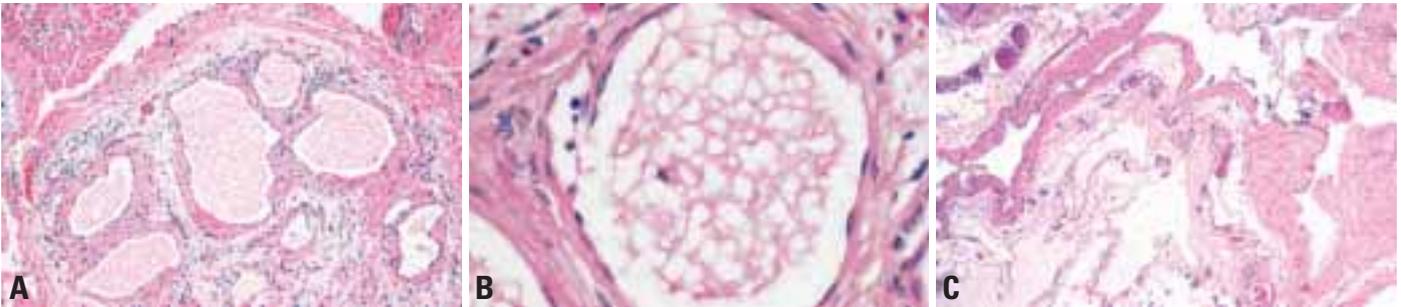


Fig. 7.12 Cavernous lymphangioma. **A** Note the prominent smooth muscle in the vessel walls. **B** There is no endothelial multilayering or atypia. **C** Note the cyst-like enlargements of lymphatic vessels.

Kaposiform haemangioendothelioma

W.Y.W. Tsang

Definition

Kaposiform haemangioendothelioma is a locally aggressive, immature vascular neoplasm, characterized by a predominant Kaposi sarcoma-like fascicular spindle cell growth pattern.

ICD-O code 9130/1

Synonyms

Kaposi-like infantile haemangioendothelioma {2135}, haemangioma with Kaposi sarcoma-like features {1554}.

Epidemiology

This is a rare tumour with no known racial predilection.

Site of involvement

The tumour most commonly occurs in the retroperitoneum {2135,2352} and the skin {1300,1554,2204}, but it can also occur in the head and neck region, mediastinum, and deeper soft tissues of the trunk and extremities {1418,2270,2352}.

Clinical features

Kaposiform haemangioendothelioma typically occurs in infancy and first decade of life, but adult cases are increasingly recognized {1300,1418}. Retroperitoneal tumours usually present as abdominal mass, ascites, intestinal obstruction, and jaundice. Deep soft tissue lesions produce single or multiple

masses and may involve the underlying bone and rarely regional lymph nodes (variably interpreted as either local extension or local metastasis) {1300}. Cutaneous lesions present as ill defined violaceous plaques. Consumption coagulopathy (Kasabach-Merritt syndrome) may complicate the larger tumours due to activation of clotting pathways within the tumour vasculature.

Aetiology

There is no known association with HIV infection or HHV8.

Macroscopy / Histopathology

Cutaneous lesions appear as ill defined,

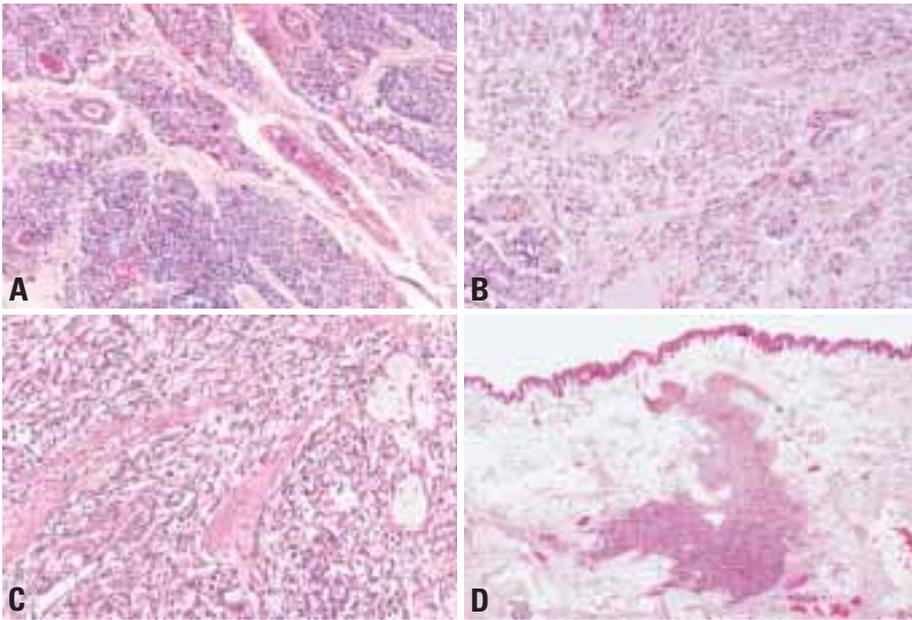


Fig. 7.13 Kaposiform haemangioendothelioma. **A** Subcutaneous lesion showing well developed lobular architecture. **B** Retroperitoneal lesion in a young infant with destructive infiltration of the pancreas. **C** Higher magnification shows loosely arranged spindle cells forming vascular slits mixed with some dilated capillaries. **D** Cutaneous kaposiform haemangioendothelioma with irregular, infiltrative tumour growth in the dermis.

violaceous plaques. Soft tissue tumours are greyish to reddish, multi-nodular, and may coalesce and encase surrounding structures.

Microscopically, the tumour grows in the form of infiltrative vague lobules separated by fibrous septa. It consists predominantly of criss-crossing spindle cell fascicles interspersed with capillaries. The fascicles are curved or straight, and may be compact with few interspersed

spaces or more loosely arranged, containing slit-like, sieve-like or crescent-shaped vascular lumens. Nuclear atypia and mitotic activity are usually inconspicuous. Rarely, the spindle cell fascicles may blend with round "glomeruloid" solid nests of polygonal / epithelioid endothelial cells which possess abundant eosino-philic cytoplasm. The interspersed capillaries are lined by flat or plump endothelial cells, and there can

be tumour lo-bules resembling cellular haemangioma or capillary haemangioma. There are often adjacent foci resembling lymphangiomatosis. Fibrin thrombi and fragmented red cells can be found in the slit-like spaces and the capillaries. There may be haemorrhage, haemosiderin deposition and rare hyaline globules.

Immunophenotype

The spindle cells are usually negative for Factor VIII-related antigen, but positive for CD34 and CD31, especially those lining vascular slits. Muscle-specific actin highlights variable numbers of spindle cells, suggesting the presence of pericytes in at least some areas.

Ultrastructure

Ultrastructural hallmarks of endothelial cells are poorly developed in the spindle cells and represented by poorly formed lumens and discontinuous basal lamina. Weibel-Palade bodies may be totally absent.

Prognostic factors

Kaposiform haemangioendothelioma shows no tendency for spontaneous regression [1300]. The prognosis varies with the site and size of the lesion. Outlook is poor for large tumours occurring in infancy complicated by Kasabach-Merritt syndrome, especially when occurring in intraabdominal sites. Lesions in the somatic soft tissue are curable by complete excision, and recurrence appears to be rare.

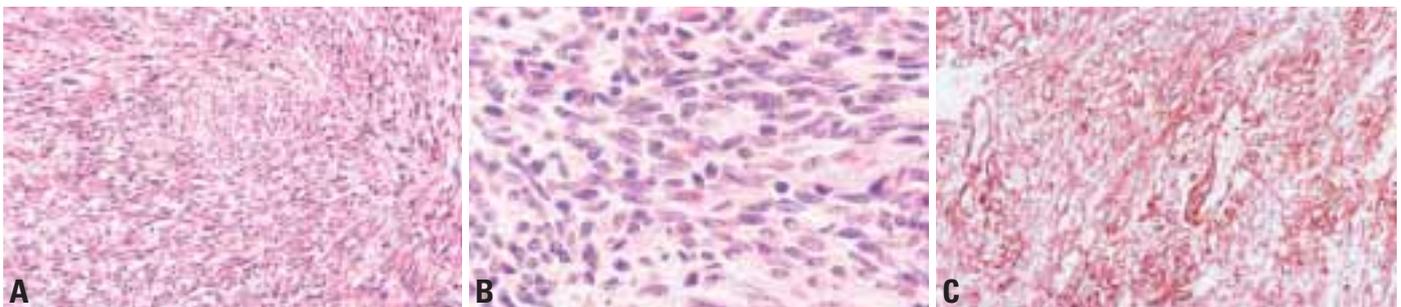


Fig. 7.14 Kaposiform haemangioendothelioma. **A** The spindle cell fascicles are compact and are interspersed with numerous capillaries. **B** The spindle cells are bland-looking. **C** The spindle cells and capillaries show strong reactivity with CD31.

Retiform haemangioendothelioma

E. Calonje

Definition

Retiform haemangioendothelioma (RH) is a locally aggressive, rarely metastasizing vascular lesion, characterized by distinctive arborizing blood vessels lined by endothelial cells with characteristic hobnail morphology. These tumours appear to be closely related to papillary intralymphatic angioendothelioma.

ICD-O code 9135/1

Synonym

Hobnail haemangioendothelioma.

Epidemiology

RH is uncommon. Since its original description in 1994, only 20 cases have been reported {296,734,1419}. The age range is wide but it usually affects young adults with no sex predominance.

Sites of involvement

The tumour involves predominantly the skin and subcutaneous tissue and shows predilection for the distal extremities, particularly the lower limb.

Clinical features

RH presents as a red/bluish slowly growing plaque or nodule usually less than 3 cm in maximum dimension. A case with multiple lesions has been described {556}. Exceptional cases occur in the setting of previous radiotherapy or pre-existing lymphoedema {296}.

Macroscopy / Histopathology

Macroscopic examination reveals diffuse induration of the dermis with frequent involvement of the underlying subcutaneous tissue. Scanning magnification reveals characteristic elongated and narrow arborizing vascular channels with a striking resemblance to the normal rete testis. Although this pattern is usually readily apparent, if the vascular channels are small or collapsed, then the retiform architecture might be difficult to recognize. Monomorphic hyperchromatic endothelial cells with prominent protuberant nuclei and characteristic tombstone or hobnail appearance line the blood vessels. These cells have scanty cytoplasm, which seems to

blend with the underlying stroma. Pleomorphism is absent and mitotic figures are rare. A prominent stromal and often intravascular lymphocytic infiltrate is present in around half of the cases. The stroma surrounding the tumour tends to be sclerotic. Focal solid areas composed of sheets of endothelial cells are often identified. Vacuolated cells are uncommonly seen. Monomorphic endothelial spindle-shaped cells are also a rare feature and were described in the single metastatic lymph node reported {296}. In some cases there are intravascular papillae with hyaline collagenous cores similar to those seen in papillary intralymphatic angioendothelioma. Retiform haemangioendothelioma can be one of the components of a composite haemangioendothelioma (see page 168).

Immunophenotype

The neoplastic cells in RH stain for vascular markers including CD31, CD34 and VWF (von Willebrand factor). Staining for CD34 is often stronger than that of other vascular markers. Most of the lymphocytes in the infiltrate stain for pan-T cell markers including CD3. Only a minority of the lymphocytes stain for the B cell marker CD20. The latter are only found in the stroma surrounding the vascular channels. In general experience these lesions are HHV-8 negative.

Prognostic factors

Multiple local recurrences (in up to 60% of cases), often over a period of many years, are the rule unless wide local excision is performed {296}. So far only one patient has been reported to develop a metastasis to a regional lymph node. A further patient developed a local soft tissue metastasis from a primary in the right big toe {1419}. To date, no patients have been described to develop distant metastasis or to die from this disease.

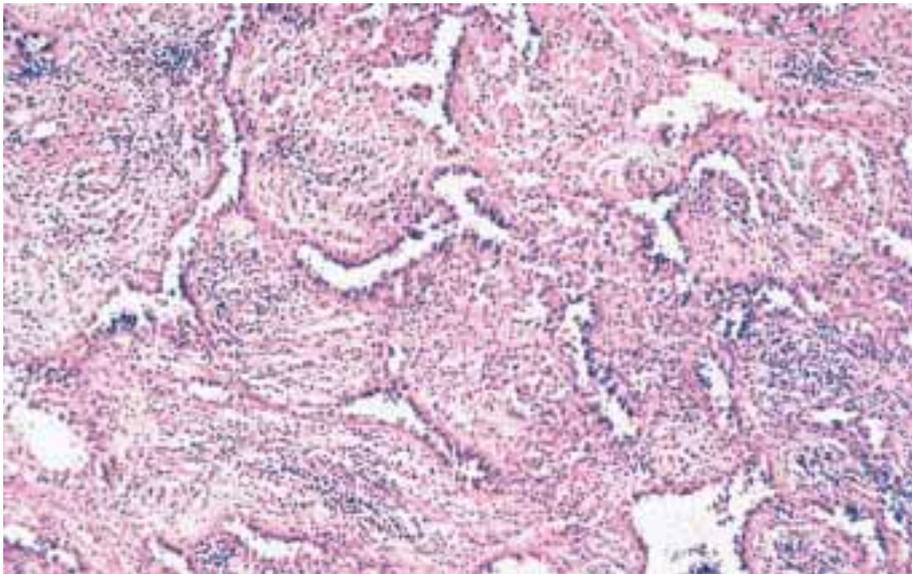


Fig. 7.15 Retiform haemangioendothelioma. Characteristic arborizing channels simulating the rete testis and with a prominent stromal lymphocytic infiltrate.

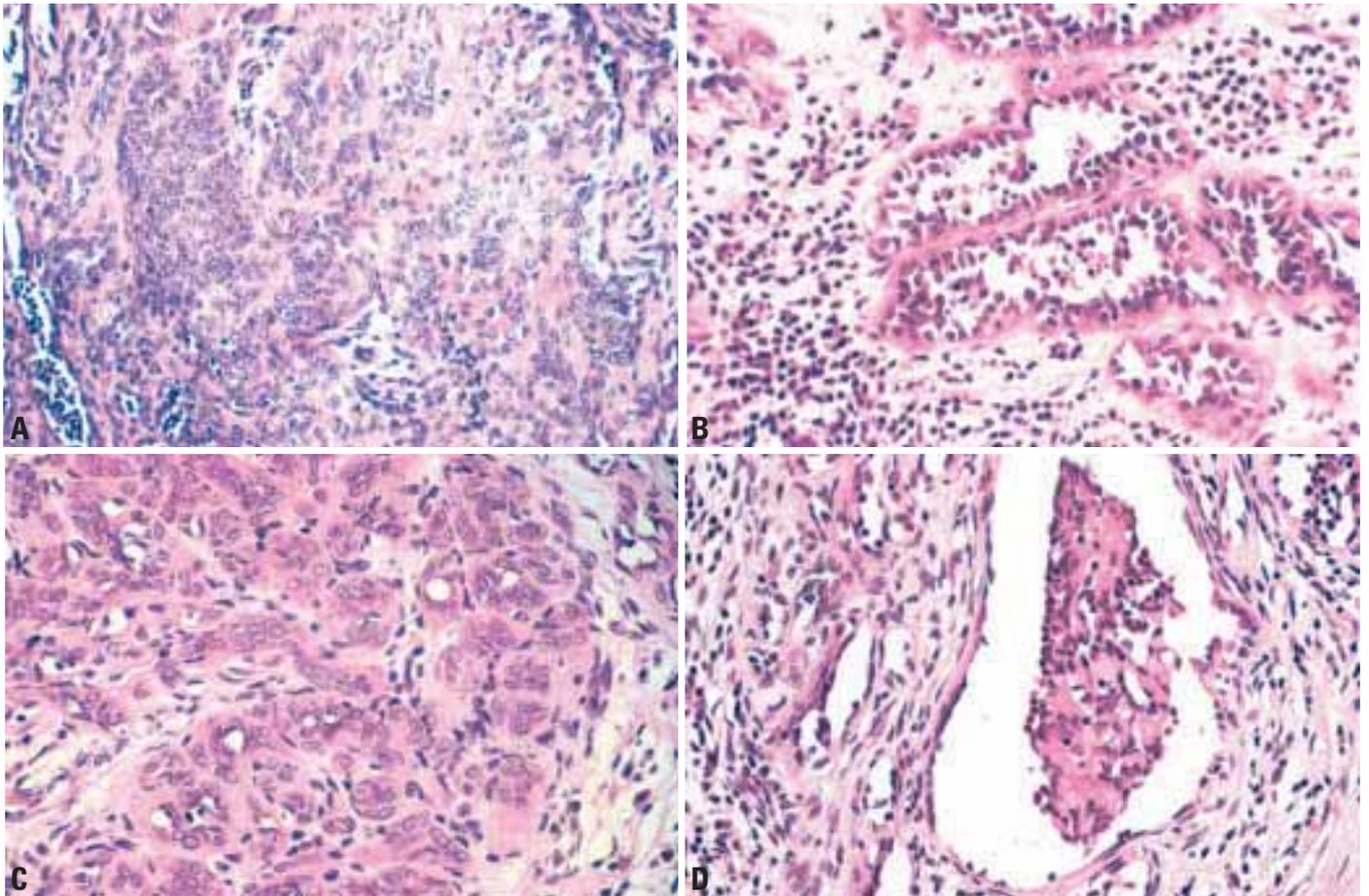


Fig. 7.16 Retiform haemangioendothelioma. **A** Focal areas with a more solid growth pattern are frequent. **B** Typical hobnail endothelial cells with prominent nuclei. **C** Vacuolated cells and **(D)** intraluminal papillae with collagenous cores similar to those seen in Dabska's tumour are seen in some cases.

Papillary intralymphatic angioendothelioma

E. Calonje

Definition

Papillary intralymphatic angioendothelioma (PILA) is a locally aggressive, rarely metastasizing vascular lesion characterized by lymphatic-like channels and papillary endothelial proliferation. These tumours appear to be closely related to retiform haemangioendothelioma.

ICD-O code 9135/1

Synonyms

Dabska tumour, malignant endothelial papillary angioendothelioma, hobnail haemangioendothelioma.

Epidemiology

PILA is very rare and has predilection for infants and children.

Around 25% of cases present in adults {635}. Sex incidence is similar.

Sites of involvement

Most cases involve the limbs and fewer cases present on the trunk.

Clinical features

PILAs present as a slowly growing asymptomatic cutaneous plaque or nodule.

Macroscopy

Tumours are ill defined and usually involve the dermis and subcutaneous tissue. The vascular nature of the lesion is not immediately apparent and haemorrhage is rare. Cystic spaces can be identified in some instances.

Histopathology

If strict diagnostic criteria are used, tumours can be described as composed of dilated, thin-walled vascular spaces often resembling a cavernous lymphangioma {635}. In rare cases the vascular channels are smaller and more irregular. Formation of prominent intraluminal papillary tufts with hyaline cores lined by hobnail endothelial cells is a characteristic finding.

The endothelial cells lining the spaces have scant pink cytoplasm and a prominent nucleus with little or no cytological atypia and a typical hobnail or matchstick appearance. The hyaline cores contain basement membrane material synthesized by tumour cells. A variable number of lymphocytes are seen within and around the vascular channels. Mitotic figures are rare.

Immunophenotype

Staining for vascular markers including CD31, von Willebrand factor and CD34 is usually positive. The finding of strong expression of vascular endothelial growth factor receptor-3 (VEGFR-3) by tumour cells in lesions with hobnail endothelial cells has been regarded as suggestive of lymphatic differentiation {635,704}. However, the specificity of this marker as an indicator of lymphatic origin is doubtful.

Prognostic factors

In the original series, a tendency for local recurrence and regional lymph node metastasis was suggested {419}. Furthermore, at least one of the patients in the original series died of disease. However, follow-up in 8 of the 12 cases reported recently reported neither local recurrences nor metastatic spread {635}. Therefore, the issue about the malignant potential of this tumour remains unsolved pending further studies. It is advisable to excise lesions widely when feasible.

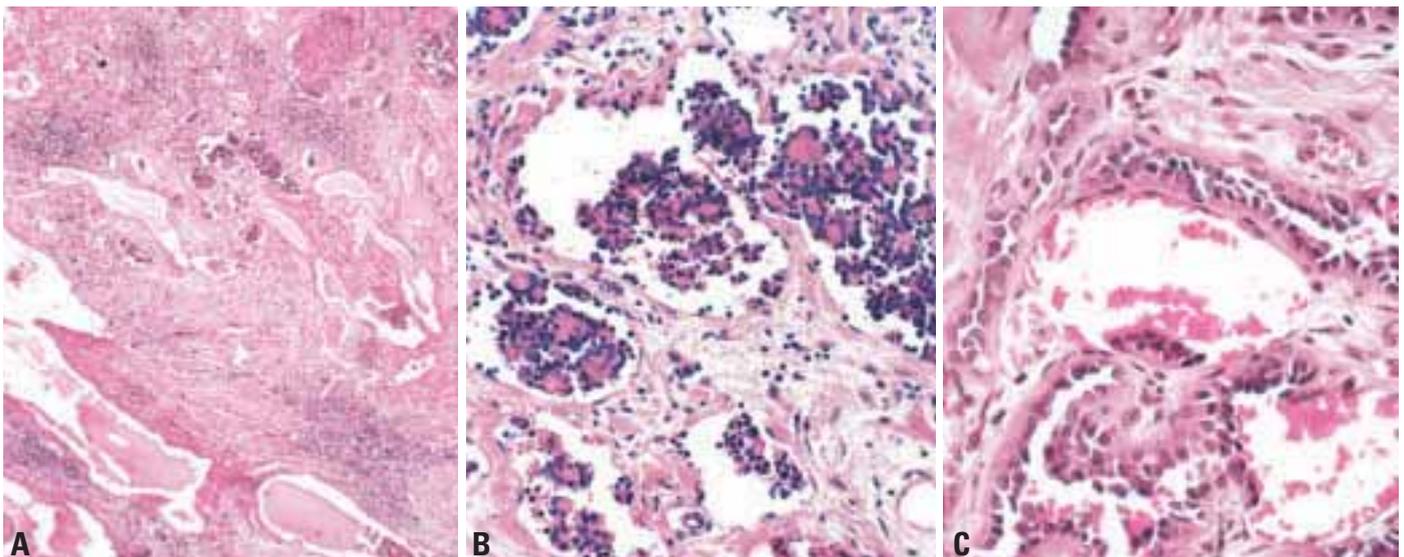


Fig. 7.17 Papillary intralymphatic angioendothelioma. **A** Cavernous lymphangioma-like spaces. **B** Numerous intravascular papillae with collagenous cores. **C** Note the characteristic hobnail epithelium.

Composite haemangioendothelioma

B.P. Rubin

Definition

Composite haemangioendothelioma is defined as a locally aggressive, rarely metastasizing neoplasm with vascular differentiation, containing an admixture of histologically benign, intermediate and malignant components.

ICD-O code 9130/1

Epidemiology

Composite haemangioendothelioma is an extremely rare and recently described neoplasm with less than 10 cases reported in the English language literature {1543,1776}. Histologically similar lesions were previously reported {373}. The gender distribution is approximately equal and the majority of cases occur in adults, although a single case which first developed in infancy has been described {1776}.

Sites of involvement

Most cases have shown a predilection for the distal extremities, especially the hands and feet, with the exception of a single case which arose in the tongue.

Clinical features

25% of patients with composite haemangioendothelioma have a history of lymphoedema. Lesions are usually long-standing (2-12 years) and have a reddish-blue, variably nodular appearance.

Macroscopy

Composite haemangioendothelioma presents as an infiltrative, uninodular or multinodular mass (individual nodules measure 0.7–6 cm), or as an area of ill defined "swelling". Some of the lesions are associated with reddish purple skin discoloration, suggestive of the diagnosis of a vascular neoplasm.

Histopathology

Composite haemangioendothelioma is a poorly circumscribed, infiltrative lesion, centered in the dermis and subcutis. It possesses a complex admixture of histologically benign and malignant vascular components that vary greatly in their relative proportions. These lesions are unified by a similar admixture of the different components which include epithelioid haemangioendothe-

lioma, retiform haemangioendothelioma, spindle cell haemangioma, "angiosarcoma-like" areas, and benign vascular lesions (arterio-venous malformation, and lymphangioma circumscriptum). Another interesting feature, seen in several cases, is the presence of large numbers of vacuolated endothelial cells which impart a pseudolipoblastic appearance. The "angiosarcoma-like" areas are characterized by a low grade angiosarcomatous appearance composed of complex dissecting vascular channels with endothelial atypia and relatively few mitotic figures. The biological significance of such lesions should be determined in larger studies. Exceptionally, the "angiosarcoma-like" area in a single case had the appearance of high grade angiosarcoma characterized by a solid growth pattern and numerous mitotic figures. The biological potential of lesions such as the latter remains to be determined through study of larger case numbers. Lesions are positive for vascular markers (CD31, CD34, and von Willebrand Factor).



Fig. 7.18 Composite haemangioendothelioma presenting as a bluish-purple multinodular mass.

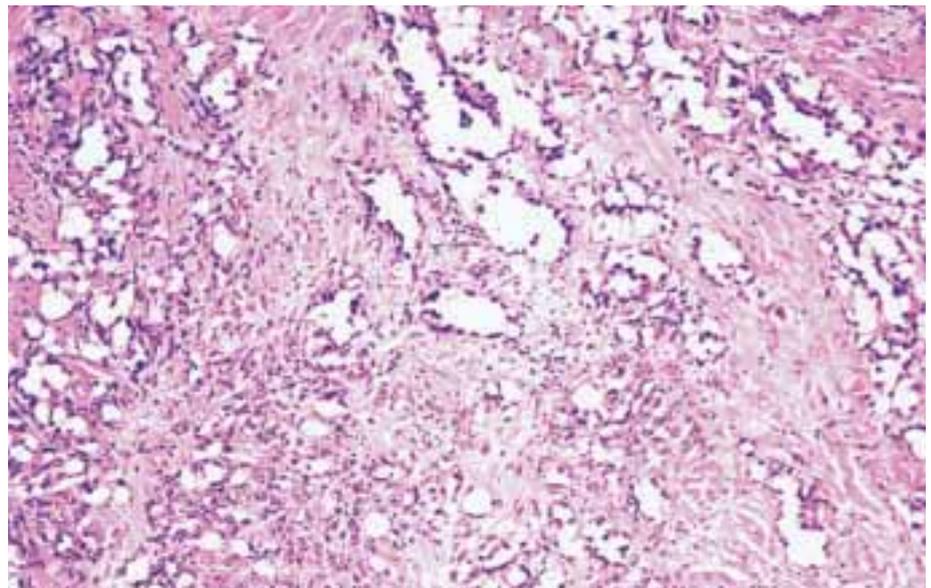


Fig. 7.19 Composite haemangioendothelioma. This complex lesion had areas consistent with retiform haemangioendothelioma as well as more solid areas consistent with epithelioid haemangioendothelioma.

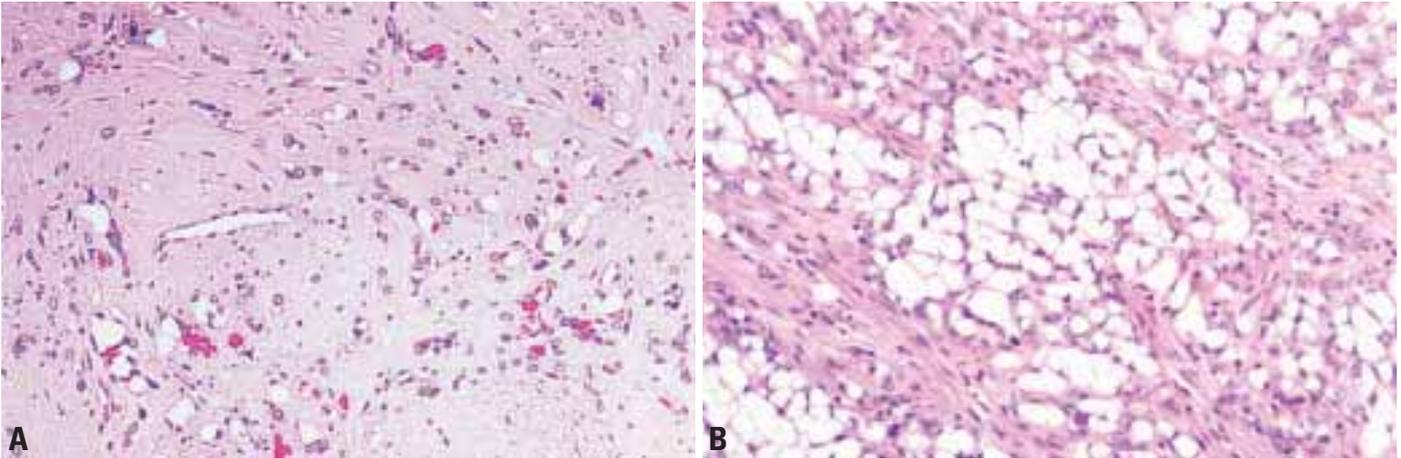


Fig. 7.20 Composite haemangioendothelioma. **A** Typical appearance of the epithelioid haemangioendothelioma component. **B** Sheets of vacuolated endothelial cells are not unusual.

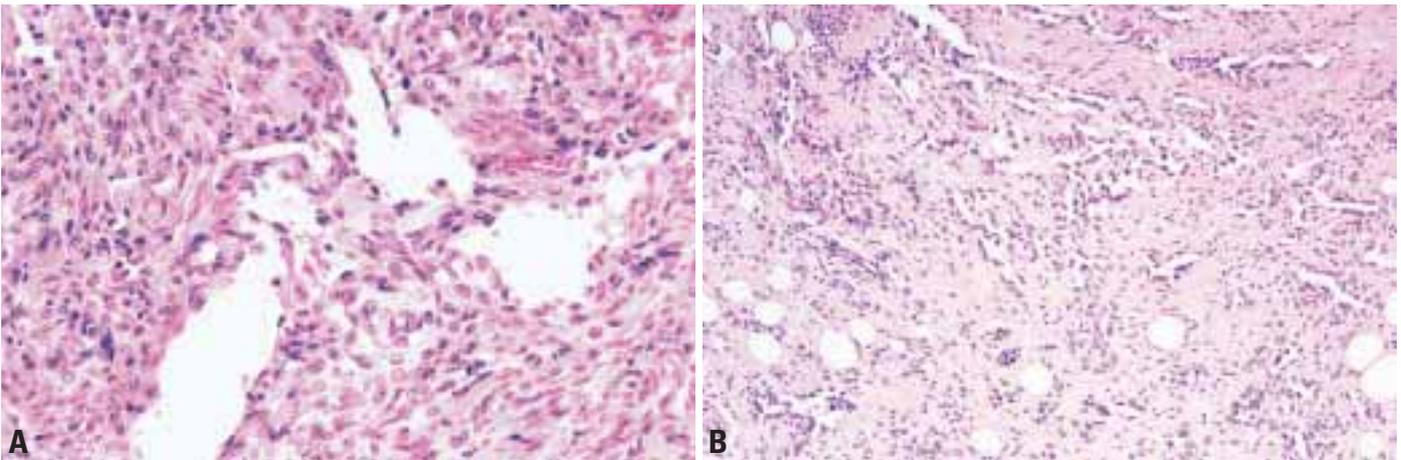


Fig. 7.21 Composite haemangioendothelioma. **A** Several lesions have areas consistent with spindle cell haemangioma. **B** Areas consistent histologically with well-differentiated angiosarcoma.

Prognostic factors

Half of the lesions recurred locally between 4 and 10 years after excision of the primary mass, often with multiple

recurrences. In the patient with the tongue lesion, metastasis occurred to a submandibular lymph node and to the soft tissue of the thigh at 9 and 11 years

after excision of the primary, respectively. Thus, the behaviour appears to be much less aggressive than conventional angiosarcoma.

Kaposi sarcoma

J. Lamovec
S. Knuutila

Definition

Kaposi sarcoma (KS) is a locally aggressive endothelial tumour that typically presents with cutaneous lesions in the form of multiple patches, plaques or nodules but may also involve mucosal sites, lymph nodes and visceral organs. The disease is uniformly associated with human herpes virus 8 (HHV-8) infection.

ICD-O code 9140/3

Synonyms

Idiopathic multiple pigmented sarcoma of the skin, angiosarcoma multiplex, granuloma multiplex haemorrhagicum, Kaposi disease.

Epidemiology

Four different clinical and epidemiological forms of KS are recognized: 1. *classic indolent form* occurring predominantly in elderly men of Mediterranean/East European descent, 2. *endemic African KS* that occurs in middle-aged adults and children in Equatorial Africa who are not HIV infected, 3. *iatrogenic KS* appearing in solid organ transplant recipients treated with immunosuppressive therapy and also in patients treated by immunosuppressive agents, notably corticosteroids, for various diseases [2127], 4. *acquired immunodeficiency syndrome-associated KS* (AIDS KS), the most aggressive form of the disease, found in HIV-1 infected individuals, that is particularly frequent in homo- and bisexual men. The relative risk of acquiring KS in the latter patients is >10,000 [800]; it

has been reduced with the advent of highly active antiretroviral therapy (HAART) [194].

Aetiology

The long sought-after infectious agent of KS was identified in 1994 by Chang et al. and was named KS-associated herpesvirus (KSHV) or human herpesvirus (HHV8) [332, 1505]. The virus is found in KS cells of all epidemiological-clinical forms of the disease and is detected in the peripheral blood before the development of KS [763,2258]; the disease itself is the result of the complex interplay of HHV8 with immunologic, genetic and environmental factors [587,1144].

Sites of involvement

The most typical site of involvement by KS is the skin. During the course of the disease or initially, mucosal membranes (e.g. oral mucosa), lymph nodes and visceral organs may be affected, sometimes without skin involvement. The involvement of a wide variety of tissues and organs has been described [1008], although KS is very rarely, if ever, seen in skeletal muscles, brain and kidney.

Clinical features

Classic type of KS is characterized by the appearance of purplish, reddish blue or dark brown macules, plaques and nodules that may ulcerate. They are particularly frequent in distal extremities and may be accompanied by lymphoedema. The disease is usually indolent, lymph node and visceral involvement occurs



Fig. 7.22 Esophageal and gastric involvement in visceral Kaposi sarcoma (KS).



Fig. 7.23 Advanced skin lesions in classic KS.



Fig. 7.24 Cutaneous Kaposi sarcoma (KS). **A** Patch lesion. **B** Plaque stage lesion. **C** Nodular stage lesion.

Table 7.01

Epidemiological-clinical types of Kaposi sarcoma.

Type	Risk groups	Skin lesions--predilection sites	Visceral involvement	Course
Classic	Elderly men of Mediterranean/ East European descent	Lower legs	Rare	Indolent
Endemic	Middle-aged men and children in Equatorial Africa	Extremities	Fairly common – adults Frequent – children (lymph nodes)	Indolent – adults Aggressive – children
Iatrogenic	Immunosuppressed patients (post-transplant, other diseases)	Lower legs	Fairly common	Indolent or aggressive
AIDS-associated	Younger, mainly homo- and bisexual HIV-1 infected men	Face, genitalia, lower extremities	Frequent	Aggressive

infrequently. Classic KS may be associated with haematopoietic malignancies.

In the *endemic form of KS*, the disease may be localized to skin and shows a protracted course. A variant of endemic disease, a lymphadenopathic form in African children is rapidly progressive and highly lethal.

Iatrogenic KS is relatively frequent. It develops in a few months to several years after the transplantation of solid organs or immunosuppressive treatment for a variety of conditions. The disease may resolve entirely upon withdrawal of immunosuppressive treatment although its course is somewhat unpredictable [2127]. Patients who develop visceral lesions may succumb to their disease [1684].

AIDS-related KS is the most aggressive type of KS. In the skin, lesions are most common on the face, genitals, and lower extremities; oral mucosa, lymph nodes, gastro-intestinal tract and lungs are frequently involved. Lymph node and visceral disease without muco-cutaneous lesions may occur. The disease commonly behaves aggressively.

While skin lesions and lymphadenopathy are obvious signs of the disease in various types of KS, the spread into visceral organs may be silent or symptomatic depending on the extent and particular location of the lesions.

Macroscopy

The lesions in the skin (patches, plaques, nodules) range in size from very small to several centimeters in diameter. The involvement of the mucosa, soft tissues, lymph nodes and visceral organs pres-

ents as haemorrhagic nodules of various sizes that may coalesce.

Histopathology

Microscopic features of all four different epidemiological-clinical types of KS do not differ. Early lesions of the skin disease are uncharacteristic and present with subtle vascular proliferation [1827]. In *patch stage*, vascular spaces are increased in number, of irregular shape, and may dissect collagen fibres in the upper reticular dermis. They often run parallel to the epidermis. The vascular

proliferation is often perivascular and periadnexal. Endothelial cells lining the spaces are flattened or more oval, with little atypia. Pre-existing blood vessels may protrude into the lumen of new vessels. Admixed are sparse lymphocytes and plasma cells; frequently, extravasated erythrocytes and deposits of hemosiderin surround the vascular structures. Slits lined by attenuated endothelial cells between collagen bundles are also seen. In some cases, there is a proliferation of spindle or oval endothelial cells around pre-existing blood vessels in the dermis.

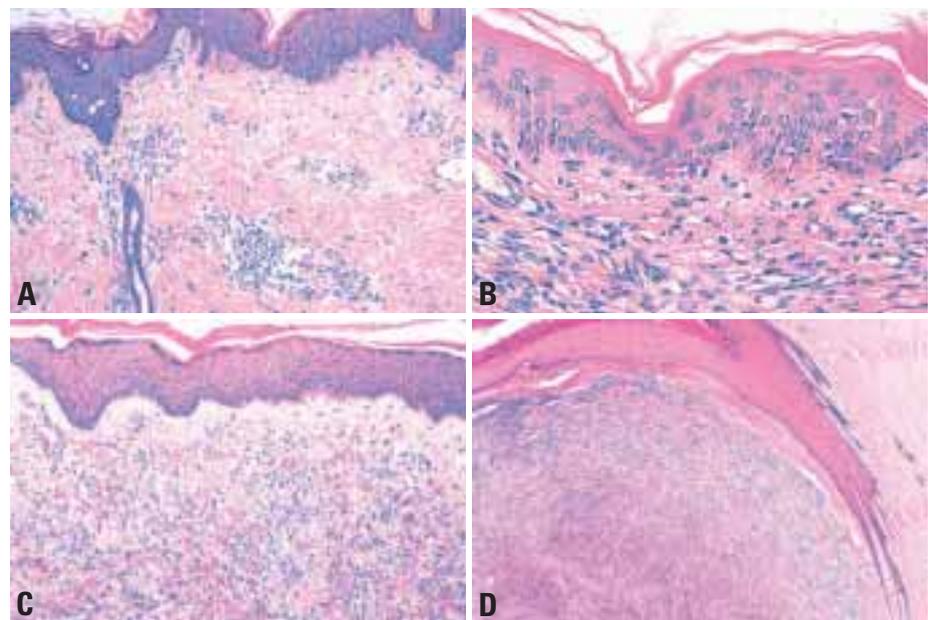


Fig. 7.25 **A** Early lesion (patch stage) in cutaneous Kaposi sarcoma (KS). **B** More cellular lesion in patch stage of cutaneous KS. **C** Marked spindle cell and vascular proliferation with extravasation of erythrocytes in early plaque stage. **D** Nodular KS of the skin; a collar of epidermis surrounds a densely cellular spindle cell tumour.

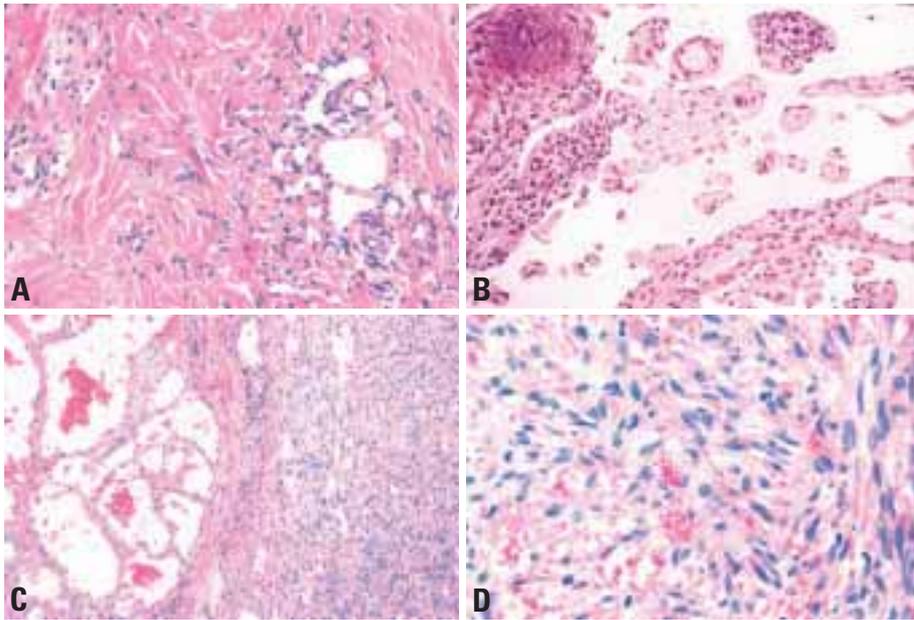


Fig. 7.26 **A** Irregular jagged vascular spaces in KS, dissecting collagen fibers of the dermis. **B** Lymph-angioma-like lesions are uncommon and morphologically deceptive. Note the accompanying plasma cells. **C** Angiomatous component in KS lesion of the skin (plaque stage). **D** High power view of nodular KS lesion; several hyaline bodies are seen.

Slit-like spaces, lymphocyte and plasma cell infiltration and extravasated erythrocytes are also observed.

In *plaque stage*, all characteristics of patch stage are exaggerated. There is more extensive angio-proliferation with vascular spaces showing jagged outlines. Inflammatory infiltrate is denser and extravascular red cells and siderophages are numerous. Hyaline globules (likely representing destroyed red blood cells) are frequently found.

Nodular stage is characterized by well defined nodules of intersecting fascicles of spindle cells with only mild atypia and numerous slit-like spaces containing red cells. Peripherally, there are ectatic blood vessels. Many spindle cells show

mitoses. Hyaline globules are present inside and outside the spindle cells. Some patients, usually with endemic nodular type KS, develop lesions which closely resemble lymphangioma.

In lymph nodes, the infiltrate may be uni- or multifocal and the lymph node may be entirely effaced by tumour. Early lesions may be subtle, showing only increased number of vascular channels accompanied by plasma cell infiltration [1287]. In visceral organs, the lesions tend to respect architecture of the organs involved and spread along vascular structures, bronchi, portal areas in the liver, etc., and from these sites they involve surrounding parenchyma [631, 1008].

Immunohistochemistry

The lining cells of clearly developed vascular structures are usually positive for vascular markers, while the spindle cells consistently show positive reaction for CD34 and commonly for CD31 but are factor VIII negative. All cases, irrespective of epidemiologic subgroup, are HHV-8 positive. The new marker FLI1, a nuclear transcription factor, appears to be expressed in almost 100% of different vascular tumours, including KS [695].

Genetics

Little is known about cytogenetic and molecular alterations in Kaposi sarcoma, but growth factors, such as VEGF/VPF and FGF most probably play an essential role in transformation [1250,1853].

Cell lines and primary tumours have been reported to have chromosome aberrations [311,1715,1838], including gain of 8q and 1q and loss of 3p, and rearrangements of 7q22, 8p11, 13q11 and 19q13. A comparative genomic hybridization (CGH) study of seven cases could not confirm these findings, but showed recurrent gains at 11q13 [1130]. Further investigation suggested that the target genes in the amplified area are *FGF4* and *FGF3* (a.k.a. *INT2*). Also *KRAS2* and *TP53* rearrangements were reported [1553,1904].

Prognostic factors

The evolution of disease depends on the epidemiological-clinical type of KS and on its clinical extent. It is also modified by treatment that includes surgery, radio- and chemotherapy. Cases with widespread visceral involvement are commonly poorly responsive to treatment.

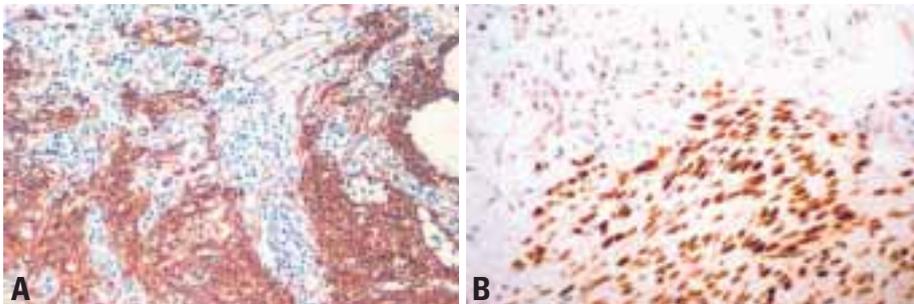


Fig. 7.27 **A** CD34 positive reaction of KS cells in nodular skin disease. **B** Nuclear immunopositivity for HHV-8 is a consistent finding in all histologic types and clinical subsets of Kaposi sarcoma.

Other intermediate vascular neoplasms

B.P. Rubin
W.Y.W. Tsang
C.D.M. Fletcher

The Working Group also considered two other tumours for possible inclusion in the new WHO classification – *polymorphous haemangioendothelioma* and *giant cell angioblastoma* – but decided that available data are insufficient to allow definitive classification of these lesions. Specifically, very few cases have been reported to date, there are as yet

no clear diagnostic criteria and there are uncertainties regarding biological potential.

Giant cell angioblastoma, of which 4 cases have been reported, arises in soft tissue of infants, is comprised of nodular aggregates of histiocytoid cells arranged around bland angiomatous vessels and may show persistent growth [808,2193].

As yet, it is not certain that this is primarily an endothelial tumour.

Polymorphous haemangioendothelioma, of which less than ten cases have been reported, may primarily involve soft tissue or lymph nodes, affects adults, has complex and worrisome morphologic features and metastasizes in some cases [327,1537,1771].

Epithelioid haemangioendothelioma

S.W. Weiss
J.A. Bridge

Definition

Epithelioid haemangioendothelioma is an angiocentric vascular tumour with metastatic potential, composed of epithelioid endothelial cells arranged in short cords and nests set in a distinctive myxohyaline stroma.

ICD-O code 9133/3

Synonyms

Intravascular bronchioloalveolar tumour, angioglomoid tumour, myxoid angioblastomatosis.

Epidemiology

Epithelioid haemangioendothelioma is a rare vascular tumour although its precise incidence has never been determined. The lesion occurs in nearly all age groups with the exception of the early childhood years and affects the sexes equally [1407, 2238, 2245].

Sites of involvement

The tumour develops as a solitary tumour in either superficial or deep soft tissue of

the extremities. Nearly one half to two-thirds originate from a vessel, usually a small vein. In exceptional cases the

lesion may arise from a large vein or artery in which case it presents as an entirely intraluminal mass.

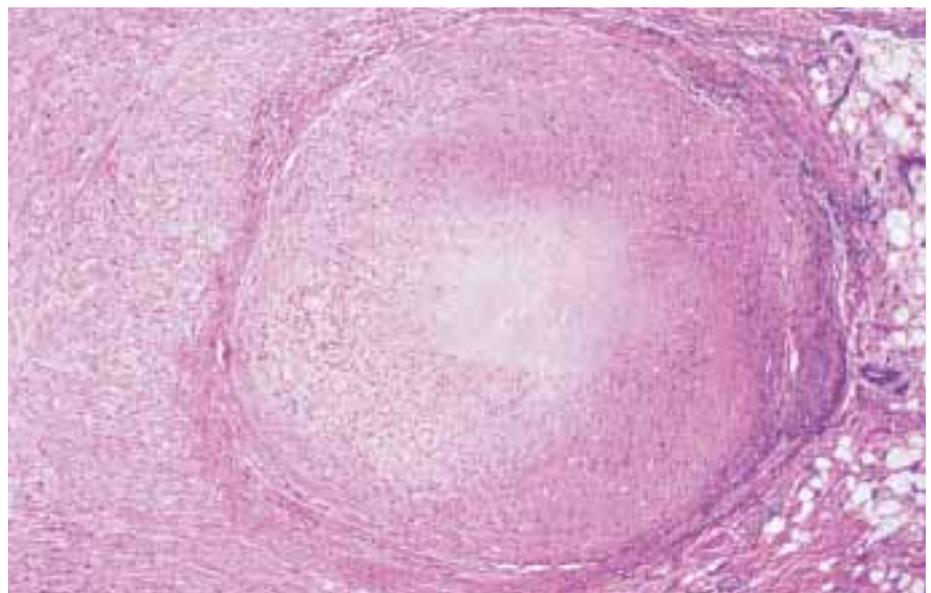


Fig. 7.28 Epithelioid haemangioendothelioma involving the lumen of a small vein and extending into adjacent tissue. Origin from a vessel is evident in approximately 30% of cases.

Clinical features

The tumour develops as an often painful nodule in either superficial or deep soft tissue. Because of its origin from a vessel there may be associated symptoms of oedema or thrombophlebitis. Deeply situated tumours may be associated with focal ossification which can be detected on plain films. Although an association with oral contraceptives has been raised with respect to hepatic forms of the disease, no such association has been documented with soft tissue variants.

Macroscopy

In its classic form, epithelioid haemangioendothelioma arises as a fusiform intravascular mass which may resemble an organizing thrombus except for the fact that it appears matted down and infiltrative of surrounding structures.

Histopathology

In small or early tumours, the lesion expands the originating vessel, preserving its architecture as it extends centrifugally into soft tissue. The lumen is filled with necrotic debris and dense collagen. Tumours are composed of short strands, cords, or solid nests of rounded to slightly spindled eosinophilic endothelial cells which have been referred to as "epithelioid" or "histiocytoid." These cells display endothelial differentiation primarily at the cellular level as evidenced by intracytoplasmic lumina (vacuoles) containing erythrocytes which distort or

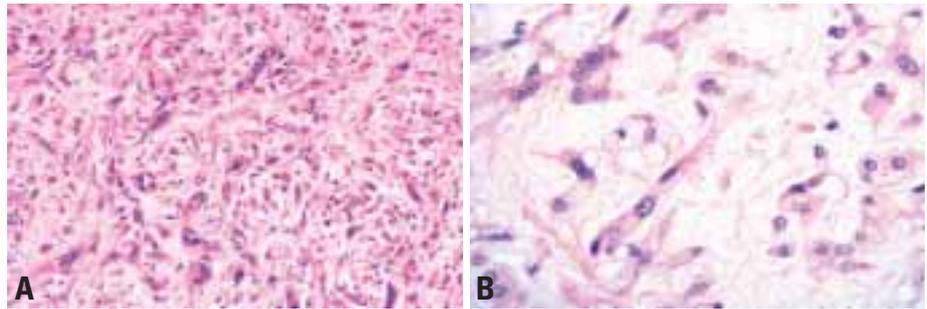


Fig. 7.29 Epithelioid haemangioendothelioma (A,B). Note the typical strand or cord-like pattern.

blister their contours. Seldom do they produce multicellular vascular channels as may be seen in epithelioid hemangiomas. The cells appear quite bland with little or no mitotic activity. The neoplastic epithelioid endothelial cells are embedded in a distinctive, sulfated acid-rich matrix which varies from a light blue (chondroid-like) to a deep pink (hyaline) colour. Metaplastic bone is occasionally present within large deep lesions and some cases contain prominent osteoclastic giant cells.

Approximately one third of epithelioid haemangioendotheliomas show atypical histologic features which confer a more aggressive course. These include marked nuclear atypia, mitotic activity (>1/10 HPF), spindling of the cells, and necrosis. These features justify the designation "malignant epithelioid haemangioendothelioma". Some cases represent a morphological continuum with epithelioid angiosarcoma.

Immunohistochemistry / Ultrastructure

A variety of vascular antigens can be identified within epithelioid haemangioendothelioma but CD31, CD34 and FLI1 are more sensitive and more reliable markers than von Willebrand factor. Focal cytokeratin expression is noted in about 25-30% of cases. By electron microscopy the neoplastic cells are situated on a distinct basal lamina, possess surface-oriented pinocytotic vesicles, and occasional Weibel-Palade bodies. They differ from normal endothelium by the abundance of intermediate (vimentin) filaments.

Genetics

An identical translocation involving chromosomes 1 and 3 [t(1;3)(p36.3;q25)] has been reported in two of three cytogenetically analysed soft tissue epithelioid haemangioendotheliomas, possibly representing a characteristic rearrangement for this entity [232,1403].

Prognosis and prognostic factors

The behaviour of epithelioid haemangioendothelioma is intermediate between haemangiomas and conventional (high grade) angiosarcomas, although the actual mortality figures are greatly influenced by inclusion of cases with atypical or malignant features in any given series. Based on studies which include both classic and malignant epithelioid haemangioendotheliomas {1407,2238,2245} the local recurrence rate is 10-15%, metastatic rate 20-30%, and mortality 10-20%. Separate analysis of classic epithelioid haemangioendothelioma lacking atypical histological features has a metastatic rate of 17% and mortality of 3% [2245]. Atypical morphological features (described above) correlate with an increased risk of metastases.

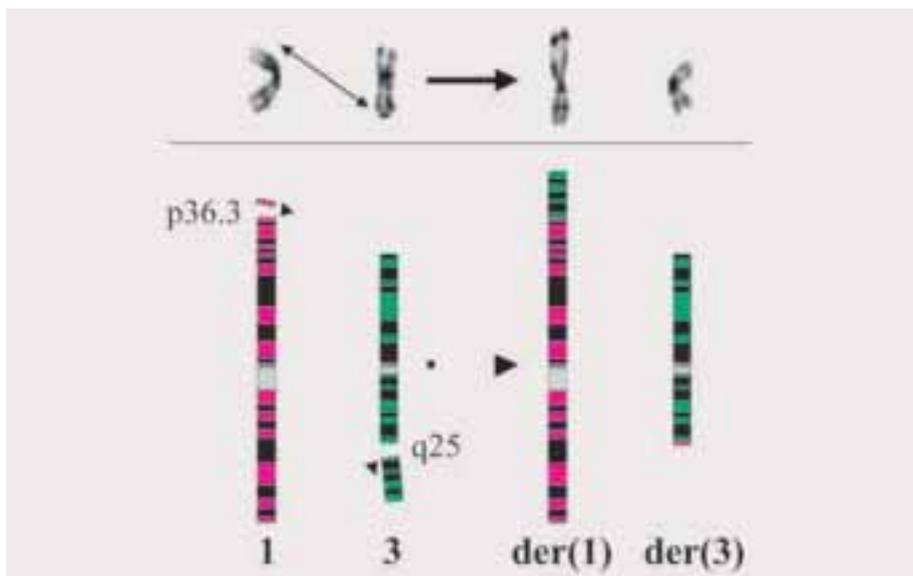


Fig. 7.30 Partial G-banded karyotype illustrating the t(1;3)(p36.3;q25) in epithelioid haemangioendothelioma.

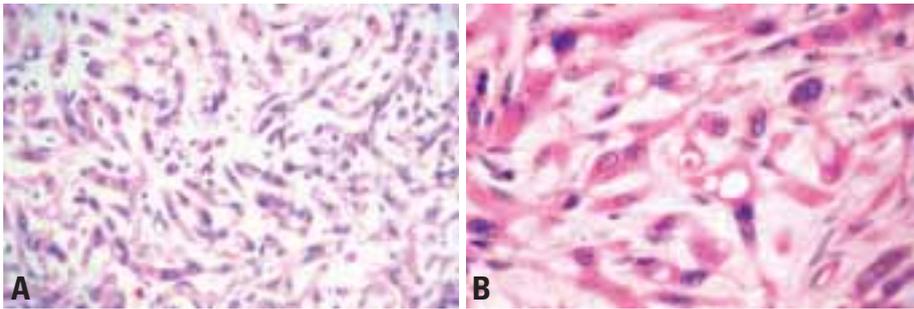


Fig. 7.31 Epithelioid haemangioendothelioma. Note (A) the myxoid matrix and (B) intracytoplasmic lumina.

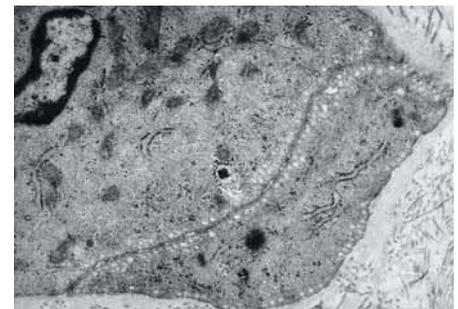


Fig. 7.32 Ultrastructure showing a prominent linear arrangement of pinocytotic vesicles and electron dense Weibel-Palade bodies.

Angiosarcoma of soft tissue

S.W. Weiss
J. Lasota
M.M. Miettinen

Definition

Angiosarcoma is a malignant tumour the cells of which variably recapitulate the morphologic and functional features of normal endothelium.

ICD-O code 9120/3

Synonyms

Lymphangiosarcoma, haemangiosarcoma, haemangioblastoma, malignant haemangioendothelioma, malignant angioendothelioma.

Incidence

Angiosarcomas are rare sarcomas the majority of which develop as cutaneous tumours sometimes associated with lymphedema (see Skin volume). Less than one quarter present as a deep soft tissue mass {1387, 2244}.

Epidemiology

Unlike cutaneous angiosarcomas, soft tissue angiosarcomas are more evenly distributed throughout the decades with a peak incidence in the 7th decade. Angiosarcomas occurring in childhood, however, are very rare.

Sites of involvement

Most lesions occur in the deep muscles of the lower extremities (about 40%) followed by the arm, trunk and head and neck. A significant proportion arise in the abdominal cavity. Rarely the lesions are multifocal.

Clinical features

Soft tissue angiosarcomas develop as enlarging masses which in one third of patients are also associated with other symptoms such as coagulopathy, anaemia, persistent haematoma, or bruisability. In very young patients high output cardiac failure from arteriovenous shunting or even massive haemorrhage may be observed. About one third of patients develop these tumours in association with certain pre-existing conditions suggesting several pathogenetic mechanisms in the development of this form of angiosarcoma. For example, soft tissue angiosarcomas have been reported within benign or malignant nerve sheath tumours associated with neurofibromatosis (NF1), adjacent to synthetic vascular grafts or other foreign material, in rare benign haemangiomas, in

patients with Klippel-Trenaunay and Maffucci syndromes, and following radiation for various types of malignancies.

Macroscopy / Histopathology

These lesions are multinodular haemorrhagic masses that range in size from a few centimeters to several centimeters in diameter. They vary in appearance from spindle to epithelioid neoplasms. Thus, at one extreme an angiosarcoma may resemble a fibrosarcoma or Kaposi sarcoma or at the other extreme an undifferentiated carcinoma. Angiosarcomas with either one of these extreme appearances may be very difficult to diagnose on light microscopy without the benefit of ancillary studies (see below). Generally angiosarcomas in soft tissue have both epithelioid and spindled areas with an emphasis on the former. Epithelioid areas are made up of large rounded cells of relatively high nuclear grade which are arranged in sheets, small nests, cords or rudimentary vascular channels. The diagnosis of angiosarcoma is suspected on light microscopy by identifying cells forming rudimentary vascular channels. Unlike normal vascular channels, these

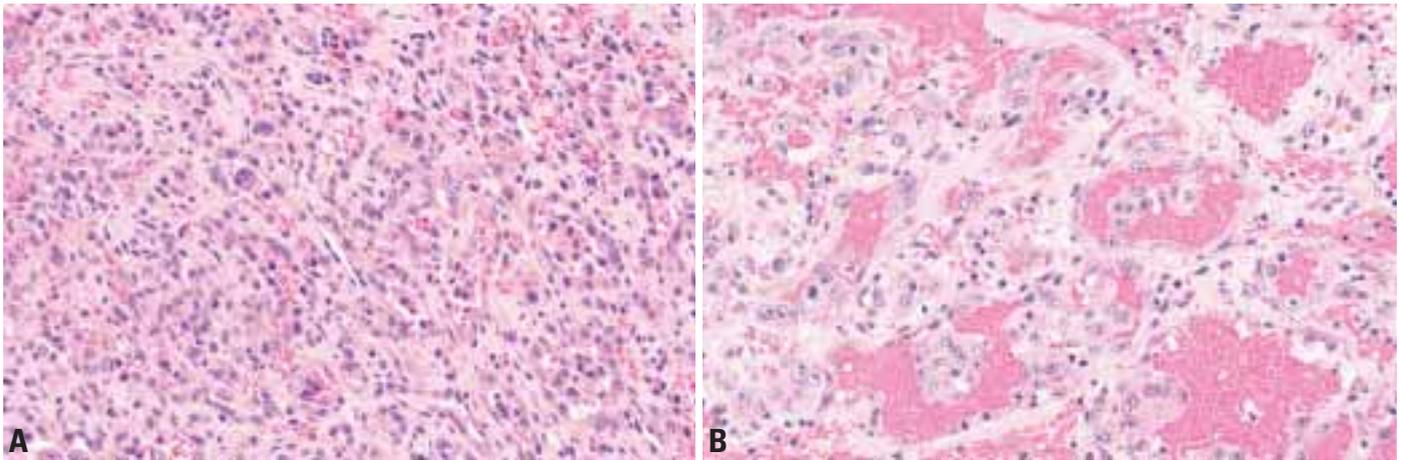


Fig. 7.33 Angiosarcoma (A,B). Many cases in soft tissue have predominantly epithelioid cytomorphology with variably solid or vasoformative architecture.

neoplastic channels are irregular in shape, freely intercommunicate with one another in a sinusoidal fashion, and infiltrate surrounding tissues in a destructive fashion. In some areas the vessels may be lined by a single attenuated layer of neoplastic endothelium resembling a haemangioma while in other areas the vascular channels are lined by a surfeit of neoplastic endothelium forming intraluminal buds, projections or papillae. Extensive haemorrhage is a characteristic feature of most tumours, and, in the extreme case, a haemorrhagic soft tissue angiosarcoma may masquerade as a chronic haematoma.

The majority of soft tissue angiosarcomas are high grade tumours characterized by cells of high nuclear grade displaying mitotic activity. In occasional cases, however, areas with low grade, sometimes epithelioid morphology may be observed. These areas can be noted,

but the overall diagnosis should usually reflect the diagnosis of a high grade angiosarcoma.

Epithelioid angiosarcoma

Epithelioid angiosarcoma is a variant of angiosarcoma composed predominantly or exclusively of large rounded "epithelioid" endothelial cells with abundant amphophilic or eosinophilic cytoplasm and large vesicular nuclei [681]. Architecturally the cells are arranged in the patterns described above. Although these lesions may occur as cutaneous tumours, most segregate in deep soft tissue. Many cases express cytokeratin along with endothelial markers. Their principal significance is the close mimicry they provide with carcinoma.

Immunohistochemistry

Immunohistochemistry is an important adjunctive procedure in the diagnosis of

angiosarcoma, particularly for poorly differentiated forms in which vascular channel formation is difficult to identify. Angiosarcomas express to a greater or lesser degree the usual vascular antigens including von Willebrand factor, CD31, and CD34. Although von Willebrand factor is the most specific of the vascular markers, it is also the least sensitive, often present in only a minority of angiosarcomas as focal weak staining. CD31, on the other hand, combines both relative specificity with excellent sensitivity and is positive in approximately 90% of angiosarcomas of all types [477, 2244]. Cytokeratin is present in about one third of soft tissue angiosarcomas, particularly in the epithelioid forms, reflecting the fact that cytokeratin cannot be used as an absolute discriminant between angiosarcoma and carcinoma. Although not regarded as "first line" antigens, in the diagnosis of angiosarcomas,

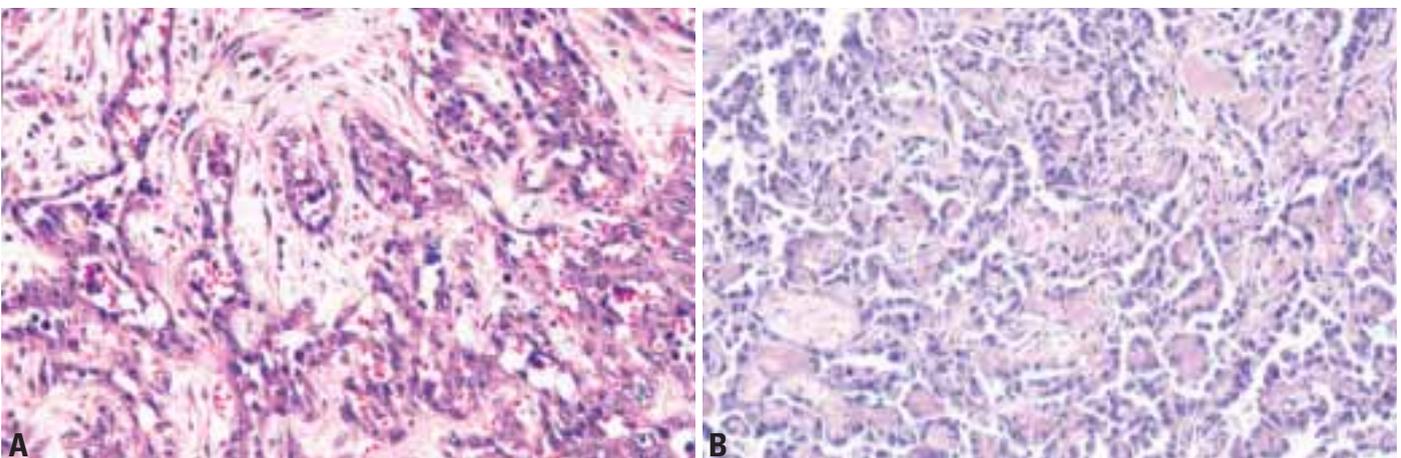


Fig. 7.34 Angiosarcoma (A,B). These lesions show more obvious vasoformative growth with complex anastomosing channels.

laminin and Type IV collagen can be detected around neoplastic vascular channels and, therefore, can be used to accentuate vascular channel formation not readily apparent by light microscopy. Actin likewise identifies pericytes which partially invest the vascular channels in angiosarcomas. In general experience angiosarcomas are consistently HHV-8 negative.

Ultrastructure

In better differentiated areas of angiosarcoma, clusters of neoplastic cells surrounded by basal lamina and occasional pericytes can be identified. The neoplastic cells are joined by junctional attachments and possess abundant intermediate filaments, sparse to moderate rough endoplasmic reticulum mitochondria and Golgi apparatus, and have surface oriented pinocytotic vesicles. Weibel-Palade bodies, a specific tubular organelle of normal endothelium, are only rarely identified [1387].

Genetics

Genetic studies of soft tissue angiosarcomas are scant and limited to isolated cases.

Almost all reported angiosarcoma karyotypes have shown complex cytogenetic aberrations {320,787,929,1120,1489,1896,2293,2349}. The only exception is a karyotype obtained from angiosarcoma arising in cavernous haemangioma, showing trisomy 5 and loss of the Y as the sole cytogenetic abnormalities [1321]. No consistent, recurring chromosomal abnormality has yet been identified. However, some cytogenetic changes reported in tumours

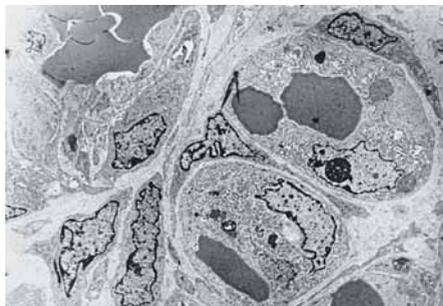


Fig. 7.36 High grade angiosarcoma with epithelioid features showing an ill-formed vessel lined by plump endothelial cells and containing erythrocytes.

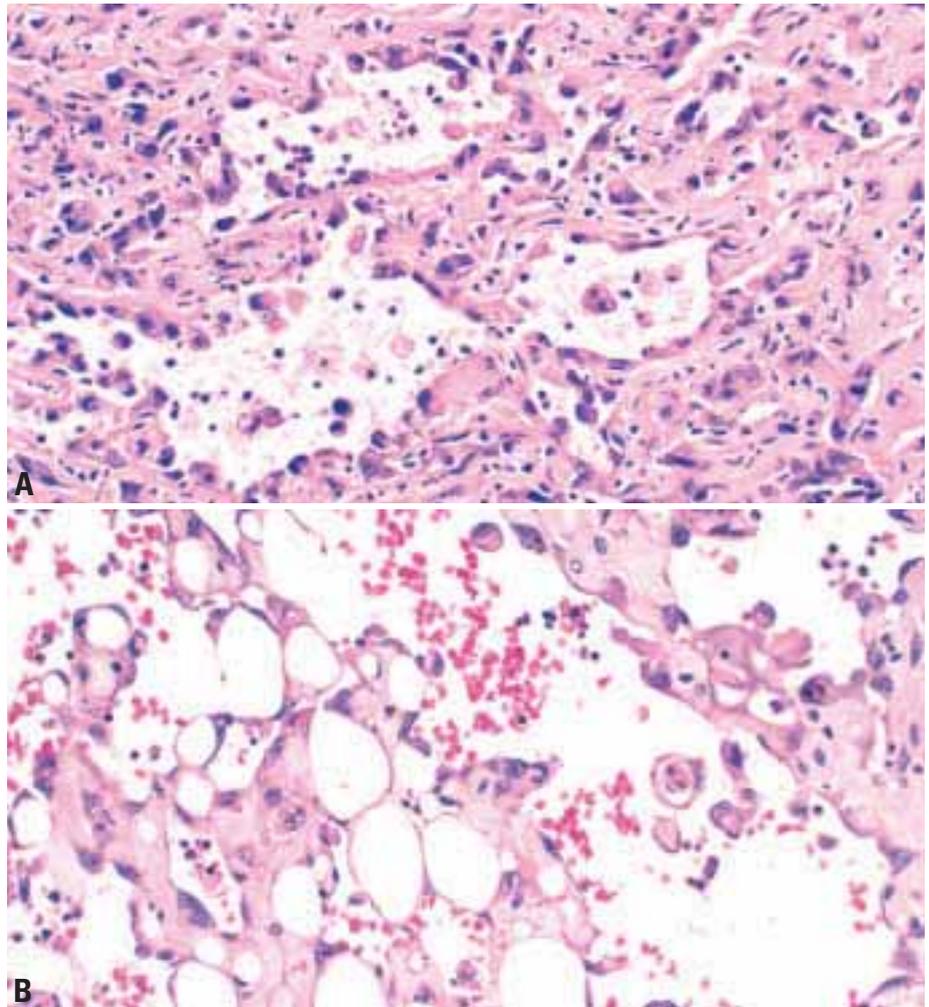


Fig. 7.35 Angiosarcoma (A,B). Note endothelial papillae and the dissecting growth pattern.

from different locations revealed similarities. Among the most common changes were gains of 5pter-p11, 8p12-qter, 20pter-q12 and losses of 4p, 7p15-pter, -Y and abnormalities involving 22q {320, 787, 929, 1120, 1321, 1896, 2293, 2349}.

Flow cytometric DNA studies have shown diploid, tetraploid and aneuploid patterns [521, 614, 739]. No significant correlation between clinical outcome and DNA ploidy pattern has been reported [521,614,739].

Association between exposure to thorium dioxide or vinyl chloride and development of liver angiosarcoma is well known. Specific *KRAS2* and *TP53* mutations were identified in these tumours [963, 1330,1331,1527,1734,1981,2129]. Similar *KRAS2* and *TP53* mutations were

also reported in sporadic skin / soft tissue and parenchymal angiosarcomas [1527,1734,1981,2344]. An alteration of the *TP53 / MDM2* pathway with elevated expression of TP53 and MDM2 proteins was documented in 60% of angiosarcomas [2344].

Prognostic factors

Soft tissue angiosarcomas are highly aggressive tumours. Local recurrences develop in about one fifth of patients and one half may be expected to die within the first year after diagnosis with metastatic disease in the lung followed by lymph node, bone, and soft tissue. The features which have been statistically correlated with poor outcome include older age, retroperitoneal location, large size, and high Ki-67 values [1387].