



CHAPTER 9

Tumours of Uncertain Differentiation

In the past, tumours in this category were often labelled as being of 'uncertain histogenesis'. However, a histogenetic concept for mesenchymal neoplasms is no longer regarded as tenable and there is little or no evidence that connective tissue tumours arise from their normal cellular counterparts. Instead we now think in terms of line of differentiation, which is determined by patterns of gene expression. For tumours in this category, in most cases we have no clear idea as to the line of differentiation (or normal cellular counterpart) that these lesions are recapitulating. Conversely, in some cases (e.g., mixed tumour, synovial sarcoma and clear cell sarcoma), we can identify a line of differentiation but we are unable to define a cellular counterpart in normal mesenchymal tissues.

Principal changes and advances in the category since the 1994 WHO classification are the addition of several newly-recognized entities, including pleomorphic hyalinizing angiectatic tumour, mixed tumour / myoepithelioma in soft tissue and PEComa, as well as the allocation of the angiomatoid fibrous histiocytoma and extraskeletal myxoid chondrosarcoma to this category. As the occurrence of divergent differentiation in a variety of other sarcoma types has become better defined, the category of malignant mesenchymoma seems gradually to be disappearing.

Extraskeletal Ewing sarcoma / peripheral primitive neuroectodermal tumour, now acknowledged to be a single definable entity with a variable degree of neuronal differentiation, is described in the Bone section of this volume.

Intramuscular myxoma

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Definition

Intramuscular myxoma is a benign soft tissue tumour characterized by bland spindle shaped cells embedded in hypovascular, abundantly myxoid stroma. Intramuscular myxomas may have areas of hypercellularity and increased vascularity ("cellular myxoma"). Mazabraud syndrome is the combination of intramuscular myxoma(s) and skeletal fibrous dysplasia.

ICD-O code 8840/0

Epidemiology

Intramuscular myxoma has a predilection for females and most patients are 40 to 70 years of age at the time of diagnosis.

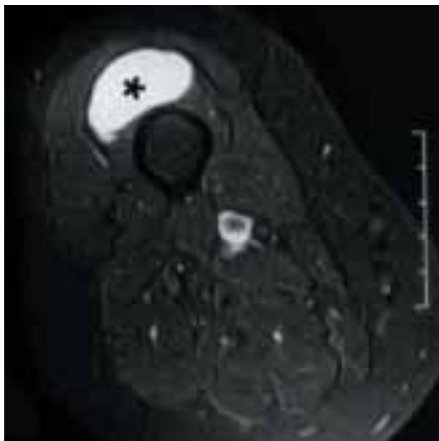


Fig. 9.01 Intramuscular myxoma. MRI reveals a well-circumscribed, hyperintense tumour (*) adjacent to the tibia.



Fig. 9.02 Intramuscular myxoma showing a gelatinous mass with internal septa. The tumour appears well-circumscribed, but closer inspections shows some infiltration of the surrounding skeletal muscle.

Sites of involvement

The most frequent sites affected are the large muscles of the thigh, shoulder, buttocks and upper arm.

Clinical features

Patients usually complain of a painless soft tissue mass. Angiographic studies reveal a poorly vascularized tumour {1119}. Magnetic resonance imaging studies show that the tumour is bright on T2-weighted images and has low signal intensity relative to skeletal muscle on T1-weighted images {1171,1900}.

Macroscopy

Grossly, the tumours have a gelatinous, lobulated cut surface. They can measure up to 20 cm {904}, however most tumours are between 5 and 10 cm in greatest diameter. Although intramuscular myxomas may appear well circumscribed, closer inspection often reveals ill defined borders with the tumour merging with the surrounding skeletal muscle. Fluid filled cystic spaces may be present.

Histopathology

The classic intramuscular myxoma is composed of uniform and cytologically bland spindle and stellate shaped cells with tapering eosinophilic cytoplasm and small nuclei {591,1448}. The cells are separated by abundant myxoid extracellular stroma containing very sparse capillary sized blood vessels. The stroma may be vacuolated and may show cystic change. In some areas a fibrous capsule may surround the tumour. Sections from the interface of the tumour and the surrounding skeletal muscle frequently shows infiltration between muscle fibres or around individual skeletal muscle cells, which may be atrophic. Areas of increased cellularity are present in many intramuscular myxomas and they can occupy 10 to 90% of the tumour {1562, 2182}. Increased number of cells, and more numerous collagen fibres and blood vessels characterize these areas and, if this pattern predominates, then



Fig. 9.03 X-ray from a patient with Mazabraud syndrome. AP view of the entire femur and pelvis shows multifocal lytic lesions with thin sclerotic margins involving the wing of the ilium, the acetabulum, the pubis and the femur which shows "shepherd's crook deformity".

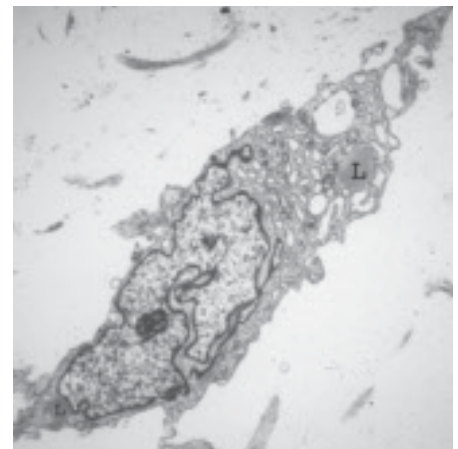


Fig. 9.04 Intramuscular myxoma. EM shows predominantly fibroblastic differentiation; the cells have abundant dilated rough endoplasmic reticulum and occasional intracytoplasmic lipid droplets (L).

the term '*cellular myxoma*' may be used {2182}. Mitoses, pleomorphism, hyperchromasia or necrosis are not present even in the most cellular areas {1562, 2182}. The vessels in these hypercellular regions are capillary sized but occasional thick walled vessels with smooth muscle in their walls are also present.

Immunophenotype

Immunohistochemically the cells stain for vimentin and show variable staining for CD34, desmin and actin. There is no staining for S100 protein.

Ultrastructure

The tumour cells have the features of fibroblasts or myofibroblasts with prominent secretory activity. The cells contain well-developed dilated rough endoplasmic reticulum, Golgi complexes, free ribosomes, pinocytotic vesicles and occasional filaments. Also seen are more primitive appearing mesenchymal cells and histiocyte-like cells. Intracytoplasmic lipid droplets can be seen {904}.

Genetics

The only published case with abnormal karyotype displayed a hyperdiploid clone with trisomy 18 as the sole anomaly {1389}. Molecular genetic analysis has shown that point mutations of the *GNAS1* gene (a.k.a. $G_s\alpha$) seem to be common in intramuscular myxomas {1605}. Mutations in codon 211 (Arg → His and Arg → Cys) were detected in five of six intramuscular myxomas with (Mazabraud syndrome) and without fibrous dysplasia of bone {630}. *GNAS1* encodes the α -subunit of the guanine nucleotide binding protein, i.e. the G-protein that stimulates the formation of cAMP. Activating *GNAS1* mutations in codon 211 have previously also been found in certain endocrine tumours {2328}, McCune-Albright syndrome {1903}, as well as in isolated fibrous dysplasia of bone {1935}.

Prognostic factors

Conventional intramuscular myxoma is usually a non-recurrent tumour. The cellular variant has a small risk of local non-destructive recurrence {2182}.

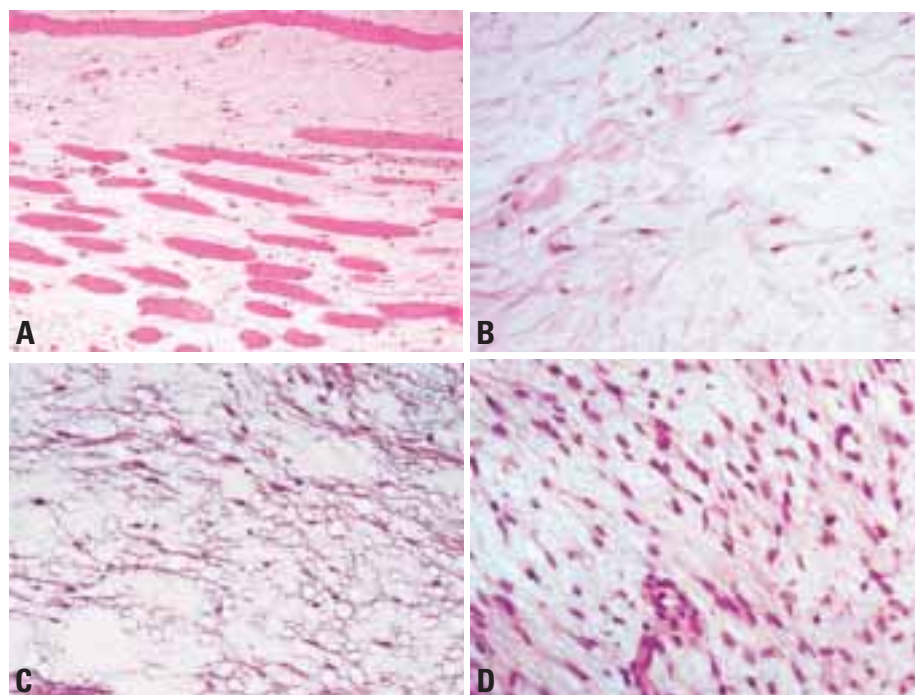


Fig. 9.05 **A** Intramuscular myxoma. At the periphery, the tumour infiltrates the surrounding skeletal muscle. **B** Intramuscular myxoma. Typically, bland spindle cells are separated by abundant extracellular myxoid matrix. **C** Intramuscular myxoma. The extracellular matrix in intramuscular myxoma may show prominent frothy appearance, mimicking lipoblasts. **D** Cellular myxoma. The cells within the cellular area are bland and do not demonstrate cytological atypia, mitoses or pleomorphism (same case as Fig. 9.06).

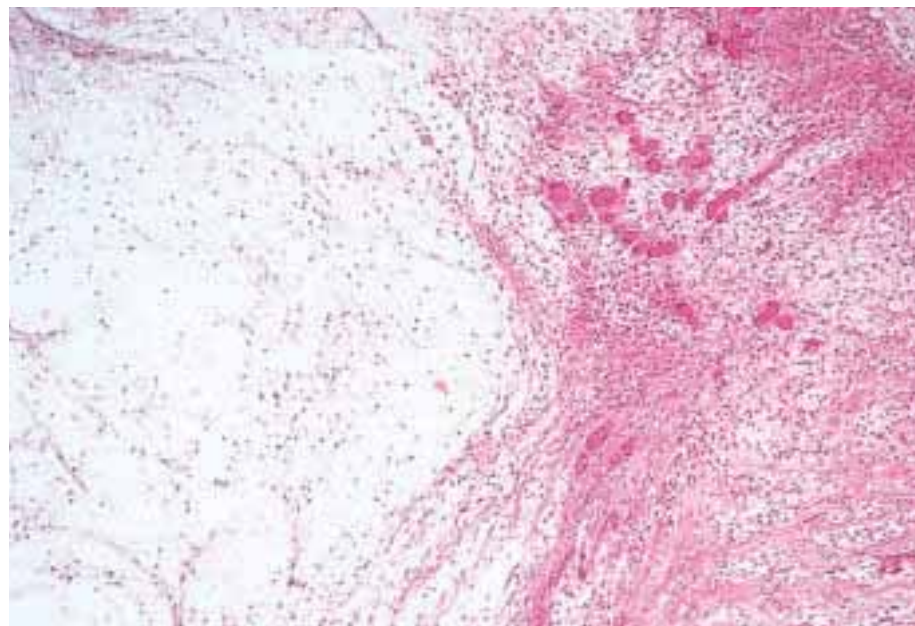


Fig. 9.06 Cellular myxoma. Classic intramuscular myxoma (left) merging with cellular myxoma (right). The former is hypocellular and hypovascular whereas the latter demonstrates increased cellularity and vascularity.

Juxta-articular myxoma

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Definition

Juxta-articular myxoma is a rare, benign soft tissue tumour that usually arises in the vicinity of a large joint, has histological features resembling a cellular myxoma, and is frequently associated with ganglion-like cystic changes.

ICD-O code 8840/0

Synonyms

Some lesions described in the literature as parameniscal cyst, periarticular myxoma, cystic myxomatous tumour around the knee, meniscal cyst and myxoid lesion associated with ganglion cysts probably represent examples of juxta-articular myxoma {41}.

Epidemiology

In the largest series the patients ranged in age from 16 to 83 years (median 43 years) {1394}; a tumour arising in a 9-year-old girl has also been reported {446}.

Sites of involvement

The majority of lesions (88%) occur in the vicinity of the knee joint. Other locations include the elbow region, shoulder region, ankle and hip.

Clinical features

The patients present with a swelling or a mass that can be painful or tender. The duration of symptoms ranges from weeks to years. Radiographic studies show a soft tissue mass that has similar imaging characteristics as intramuscular myxoma {1121}. However, the presence of haemosiderin or fibrous tissue within the lesion might suggest the possibility of pigmented villonodular synovitis or a low grade sarcoma {446}.

Macroscopy

The tumour is myxoid, slimy and gelatinous, frequently with cystic areas. The tumours range in size from 0.6 to 12 cm (mean 3.8 cm; median 3.5 cm).

Histopathology

Histologically, it is reminiscent of the cellular form of intramuscular myxoma and is composed of bland appearing spindle cells embedded in a hypovascular myxoid stroma. Although areas of increased cellularity are often present, mitotic figures are absent or very rare. Cystic, ganglion-like spaces, are seen in 89% of cases. These cystic spaces are lined by a layer of delicate fibrin or thicker layer of collagen. The periphery of the tumour

is ill defined and infiltrates adjacent tissues. Areas of haemorrhage, haemosiderin deposition, chronic inflammation, organizing fibrin and fibroblastic reaction may be seen, especially in recurrent tumours.

Immunophenotype

Same as intramuscular myxoma.

Ultrastructure

Same as intramuscular myxoma.

Genetics

Clonal chromosome abnormalities have been reported in a single case of juxta-articular myxoma {1908}. The tumour contained two unrelated clones distinguished by an $inv(2)(p15q36)$ and $+7, t(8;22)(q11-12;q12-13)$, respectively. Juxta-articular myxomas lack mutations of the *GNAS1* gene, in contrast to intramuscular myxomas {1604}.

Prognostic factors

In the series by Meis and Enzinger {1394} 10 of 29 (34%) tumours locally recurred: five recurred once, two recurred twice, two recurred three times and one recurred four times. Malignant transformation has not been reported.

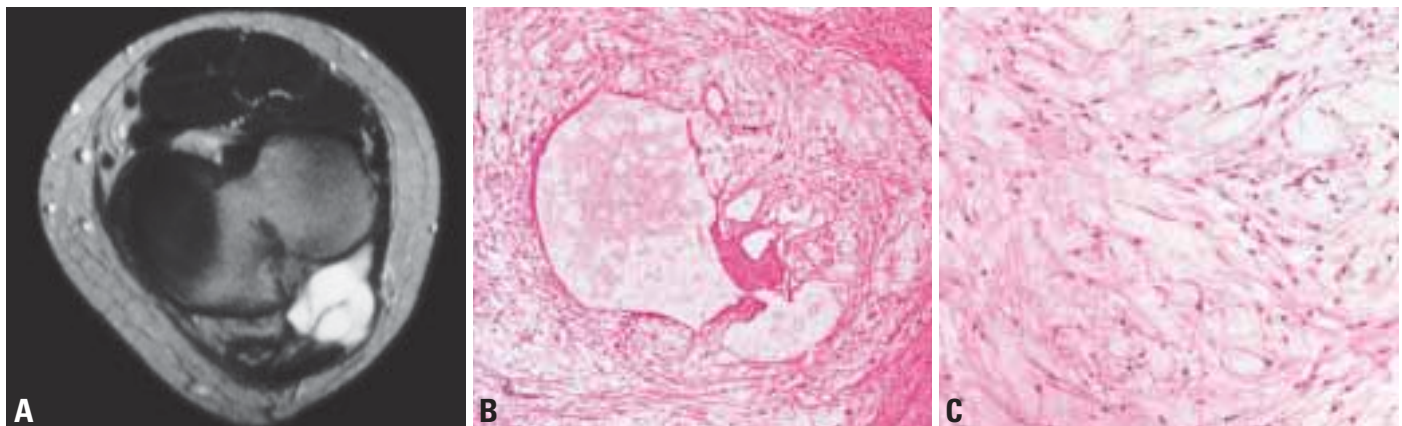


Fig. 9.07 Juxtaarticular myxoma. **A** MRI of a tumour located adjacent to the knee joint, showing a homogeneous bright signal, similar to intramuscular myxoma. **B** A cystic area filled with myxoid material is surrounded by more cellular proliferation. The cystic, ganglion like space, is lined by an eosinophilic layer of fibrin. **C** Note the bland appearance of the spindle cells.

Deep 'aggressive' angiomyxoma

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Definition

A soft tissue neoplasm with a predilection for pelvic and perineal regions and a tendency for local recurrence. It is composed of small stellate and spindle cells in a myxoedematous stroma with entrapped regional structures.

ICD-O code 8841/0

Epidemiology

Deep 'aggressive' angiomyxoma has a strong predilection for adult females in the third through sixth decades of life with a peak incidence in the fourth decade {330, 656, 826}. Elderly or postmenopausal women are only rarely affected, and the diagnosis should be viewed with suspicion in prepubertal girls. One purported example has been reported in an 11-year-old female, but the illustrations are more consistent with a superficial angiomyxoma {2260}. The tumour has also been described rarely in males with a median age at presentation in the sixth decade {367,1000,2136}.

Sites of involvement

Pelvicoperineal, inguinoscrotal, and retroperitoneal regions.

Clinical features

Most patients with deep 'aggressive' angiomyxoma present with a slow-growing mass in the pelvicoperineal region that is either asymptomatic or associated with regional pain, dyspareunia, or a pressure-like sensation {656}. The true

tumour size is often significantly underestimated by physical examination with the most common clinical impressions being a Bartholin gland cyst, vaginal cyst, hernia or lipoma. Because the bulk of the tumour is often concealed within the deep soft tissues and the process generally does not cause rectal, urethral, vaginal, or vascular obstruction, the majority of examples are quite large at the time of resection.

The imaging characteristics of this tumour are well described {1629}. CT demonstrates a hypoattenuating or isoattenuating mass that tends to grow

around pelvic floor structures, usually without causing significant disruption of the vaginal or rectal musculature. A high signal intensity is noted with T2-weighted MR images. Both T2-weighted MR and enhanced CT images also frequently demonstrate a swirled or layered internal structure. These techniques are invaluable for assessing tumour extent and determining the best surgical approach.

Macroscopy

Gross examination usually reveals a large mass, often greater than 10 cm and sometimes larger than 20 cm {656,

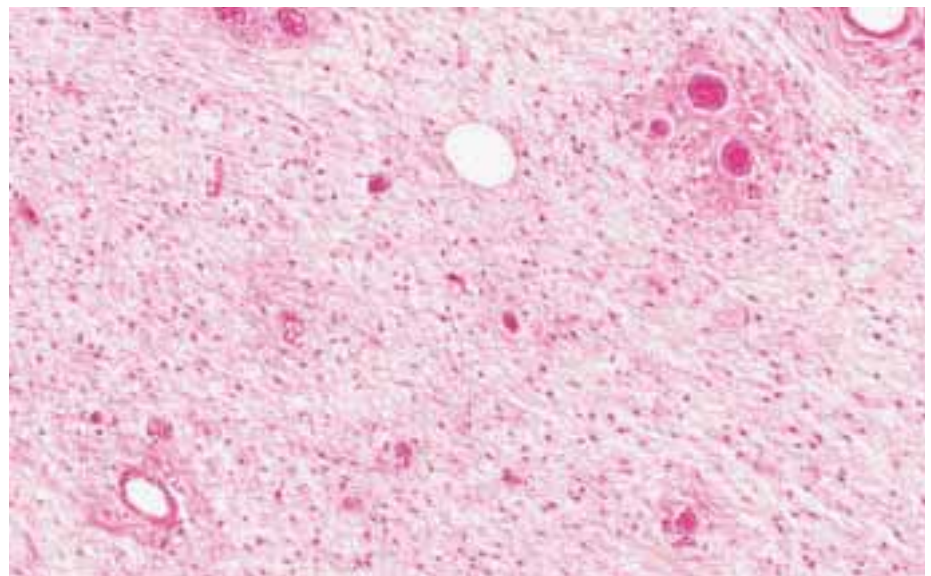


Fig. 9.09 Deep 'aggressive' angiomyxoma. Note low cellularity, hyalinized vessels, and uniform small stellate and spindle cells.

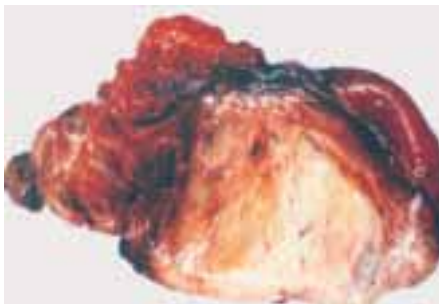


Fig. 9.08 Deep 'aggressive' angiomyxoma with whitish surface showing fibrous bands in a myxoid matrix.

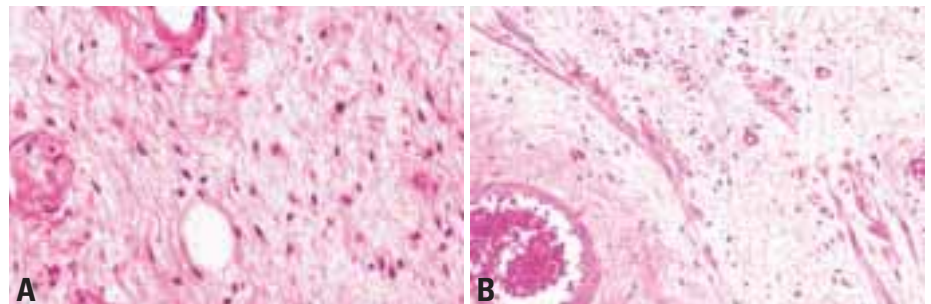


Fig. 9.10 Deep 'aggressive' angiomyxoma. **A** Small tumour cells without nuclear atypia, scattered in a fibromyxoid background. **B** Aggressive angiomyxoma with myoid cells in close proximity to vessels.

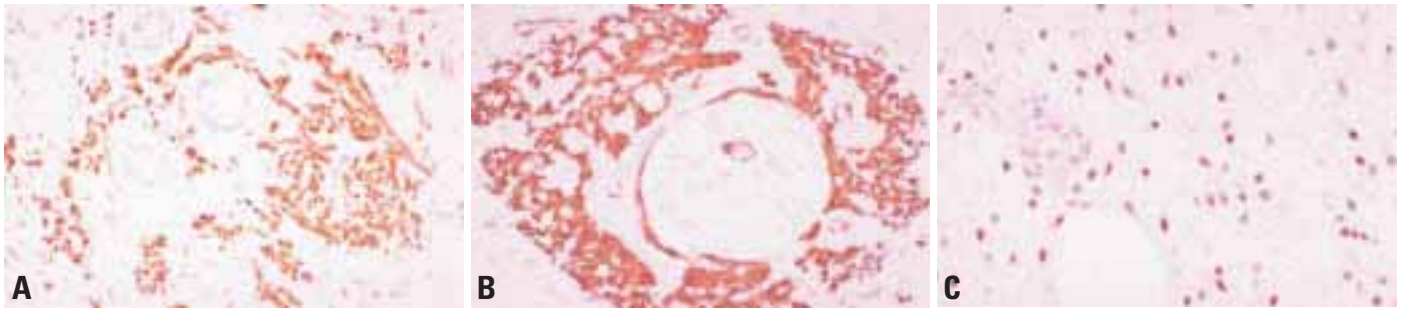


Fig. 9.11 Deep 'aggressive' angiomyxoma. Desmin (A) and smooth muscle actin (B) immunoreactivity in the myoid element. C Nuclear immunoreactivity for oestrogen receptor protein.

2024}. Small tumours under 5 cm in size are less frequent. The lesions frequently have a lobular contour with adherence to fat, muscle, and other regional structures. A soft, firm, or rubbery consistency may be present, and a glistening, myxoedematous, pink or reddish-tan cut surface is usually evident. Cystic change has occasionally been noted.

Histopathology

The tumours are of low to moderate cellularity and are composed of relatively uniform, small, stellate and spindled cells, set in a loosely collagenous, myxoedematous matrix with scattered vessels of varying caliber and entrapped regional structures. The tumour cells have scant, pale, eosinophilic cytoplasm with poorly defined borders and relatively bland nuclei with an open chromatin pattern and a single, small, centrally located nucleolus. Multinucleated cells may rarely be observed. Mitotic figures are infrequent. A characteristic finding that is seen in most cases is the presence of loosely organized islands of well-developed myoid (myofibroblastic or true smooth muscle) cells around the larger

nerve segments and vessels. Although the tumour name implies abundant myoid matrix, these neoplasms are usually only weakly positive for mucosubstances, a finding that suggests oedema fluid is a major component of the noncollagenous stroma.

Immunophenotype

The tumour cells of deep 'aggressive' angiomyxoma usually show diffuse immunoreactive for vimentin, moderate to diffuse (nuclear) immunoreactivity for oestrogen and progesterone receptor protein, and variable levels of immunoreactivity for actins and CD34 {656,826, 1369}. Desmin positivity can be identified in almost all cases. Immunoreactivity for S100 protein is absent.

Ultrastructure

Ultrastructural evaluation has revealed cells with fibroblastic, myofibroblastic, and smooth muscle features {150, 1965, 2024}.

Genetics

Cytogenetic studies have revealed clonal chromosome abnormalities in five

cases of deep 'aggressive' angiomyxoma, all affecting the female genital tract {1081, 1586}. Four tumours had abnormalities involving chromosome 12, including one case with monosomy 12 and three cases with structural rearrangements of 12q13-15. Molecular analyses of two of the cases with rearrangement of 12q13-15 identified *HMGIC* (a.k.a. *HMGGA2*) as the target gene {1081,1586}. In one case the rearrangement resulted in a fusion gene in which the first three exons of *HMGIC* were fused to ectopic sequences derived from a novel gene in 12p11.2 and in the other case the translocation breakpoint was located 3' of the gene leading to deregulation of *HMGIC* expression.

Prognostic factors

Deep 'aggressive' angiomyxoma has a local recurrence rate of approximately 30% {150, 330, 656, 826, 2024}, and such recurrences are usually controlled by a single re-excision. Thus, these tumours are less aggressive than was originally believed. These lesions have no metastatic potential.

Pleomorphic hyalinizing angiectatic tumour of soft parts

S.W. Weiss

Definition

Pleomorphic hyalinizing angiectatic tumour of soft parts (PHAT) is a non-metastasising tumour of uncertain lineage, characterized by clusters of ectatic, fibrin-lined, thin-walled vessels, which are surrounded by a mitotically inert, spindled, pleomorphic neoplastic stroma containing a variable inflammatory component.

Synonyms

There are no recognized synonyms for this distinctive lesion. Prior to the original description of this lesion in 1996 {1972} these lesions were undoubtedly misdiagnosed as schwannomas because of the ectatic vessels or as so-called malignant fibrous histiocytoma because of the degree of atypia.

Epidemiology

PHAT is characteristically a tumour arising in adults without gender predilection.

Sites of involvement

Over half of the cases arise in the subcutaneous tissues of the lower extremity, but may also occur in the subcutis of the

chest wall, buttock and arm. Only a minority develop in deep soft tissues and none to date have been reported in body cavities.

Clinical features

These tumours arise as slowly growing masses which have been present for several years before coming to medical attention. Clinically they are diagnosed as haematomas, Kaposi sarcoma or a variety of benign lesions.

Macroscopy / Histopathology

The tumours are lobulated infiltrating masses which vary from white-tan to maroon in colour. They are characterized by clusters of thin-walled ectatic vessels scattered throughout a sheet-like proliferation of spindle cells. The vessels, which range in size from small microscopic structures to macroscopic ones, tend to occur in distinct clusters. They are lined by endothelium which is lifted off the vessel wall by a subjacent coat of thick amorphous hyaline material which is largely fibrin. This material extends through the vessel wall into the surrounding stroma entrapping the neo-

plastic cells and resulting in areas of stromal hyalinization. Organising thrombus is frequently present within the vessels. The stromal cells are plump spindled and rounded cells with hyperchromatic pleomorphic nuclei often containing intranuclear cytoplasmic inclusions. Despite the level of atypia, mitotic activity is usually scant (<1 mitosis/50 HPF). A variable component of mast cells, lymphocytes, plasma cells and eosinophils may infiltrate the tumours. Psammoma bodies are occasionally present.

These tumours consistently express vimentin and occasionally CD34. Some cases show epithelial membrane antigen positivity. Notably they do not express S100 protein, making that antigen important in their distinction from schwannoma. Other antigens such as actin, desmin, cytokeratin, von Willebrand factor, and CD31 are also negative.

Clinical behaviour

About 50% of these tumours recur locally, but metastasis has not been recorded. Generally recurrences are non-destructive in their growth.

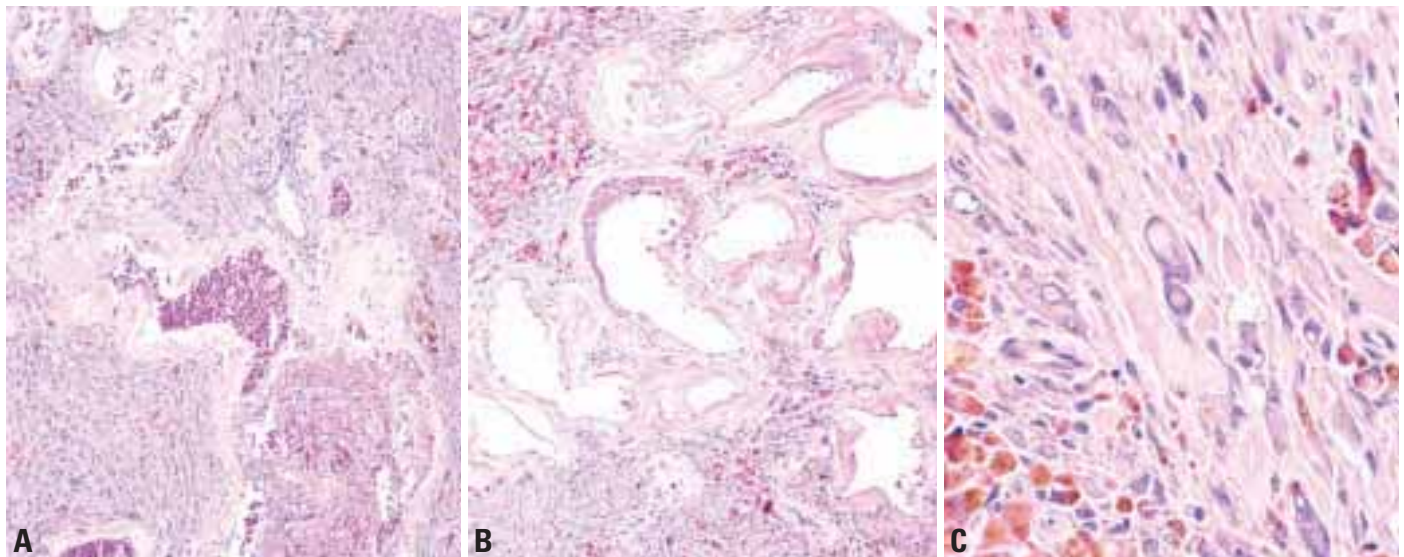


Fig. 9.12 Pleomorphic hyalinizing angiectatic tumour of soft parts. **A** Note the dilated vessels and solidly cellular areas. **B** Vessels show marked fibrinoid change in their walls. **C** Spindle cell component shows pleomorphic cells with intranuclear inclusions..

Ectopic hamartomatous thymoma

J.K.C. Chan

Definition

Ectopic hamartomatous thymoma is a benign tumour of the lower neck showing an admixture of spindle cells, epithelial islands and adipose cells suggesting branchial pouch origin.

ICD-O code 8587/0

Sites of involvement

The tumour occurs exclusively in the superficial or deep soft tissues of the supraclavicular, suprasternal or presternal region {83,328,615,660,935,1442,1806,1834,2341}.

Clinical features

The tumour affects adults with a median age of 43 years and marked male predilection (male to female ratio 8:1) {328,935,2341}. The patients present with a long-standing mass lesion.

Macroscopy

The well circumscribed tumour usually measures a few cm in diameter, but some tumours can be much larger. It shows grey-white to yellowish solid cut surfaces which may be punctuated by small cysts.

Histopathology

The tumour shows haphazard blending of spindle cells, epithelial islands and adipocytes, which are present in highly variable proportions. The spindle cells exhibit fascicular or lattice-like growth, and possess bland-looking elongated nuclei with pointed ends and light-staining cytoplasm. Some spindle cells can have a myoid appearance due to the presence of eosinophilic cytoplasm. The epithelial component takes the form of squamous islands, syringoma-like tubules, anastomosing networks, simple

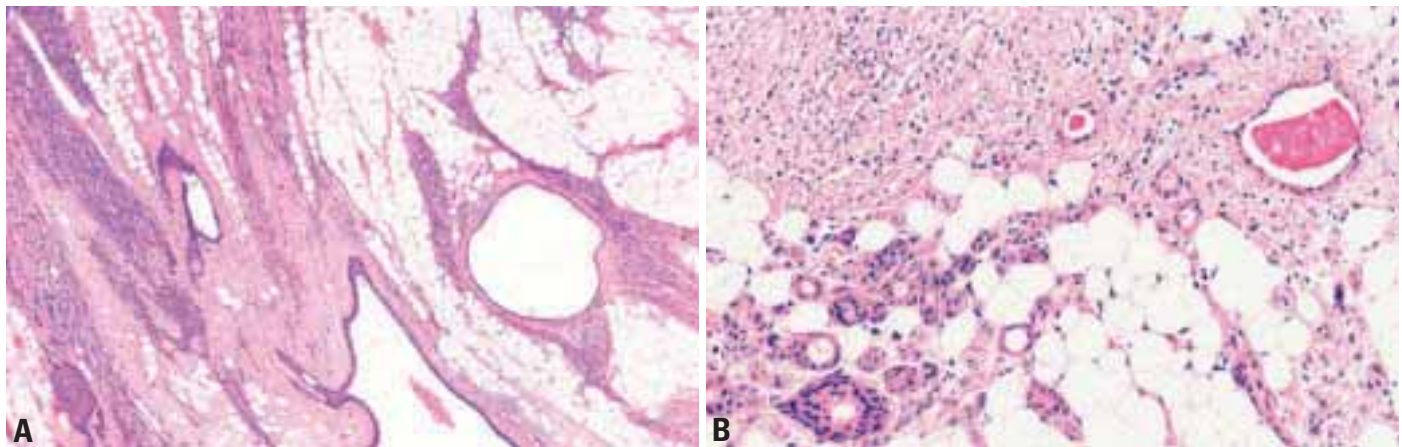


Fig. 9.13 Ectopic hamartomatous thymoma. **A** Haphazard blending of spindle cells, epithelial islands and adipose cells. Some cysts are also seen. **B** The epithelium sometimes takes the form of glandular structures. Note the presence of intermingled adipose cells.

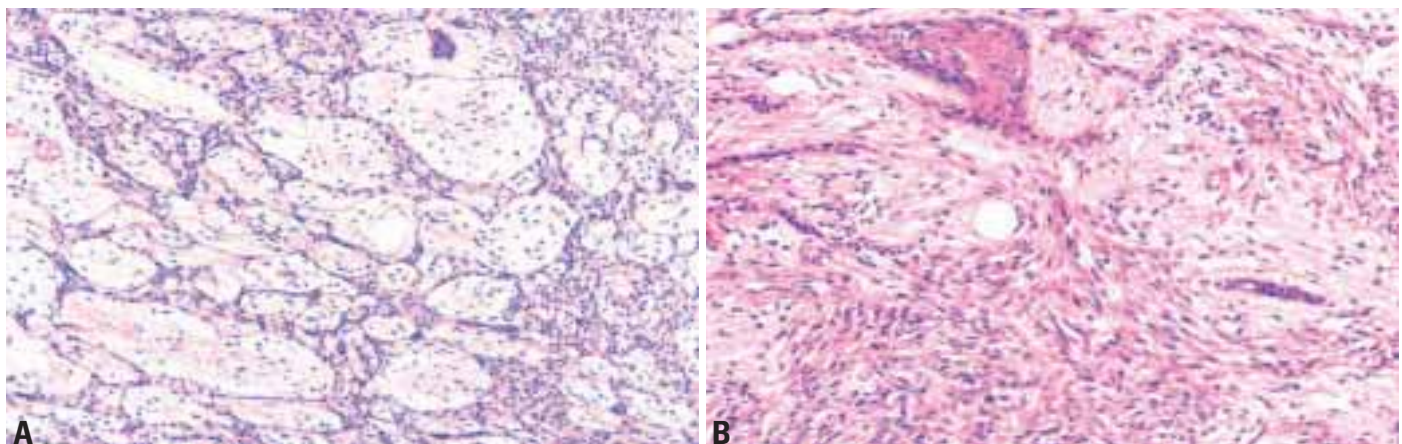


Fig. 9.14 Ectopic hamartomatous thymoma. **A** The spindle cells commonly exhibit lattice-like growth, reminiscent of atrophic thymus. **B** Characteristically elongated strands of epithelium merge into spindle cells. The epithelium commonly shows squamous differentiation.

glandular structures and cysts. The epithelial islands are surrounded by a fibrous sheath or merge imperceptibly into the spindle cells.

Immunophenotype

Both the epithelial and spindle cell components stain diffusely and strongly for cytokeratin, in particular high molecular weight cytokeratin, indicating that the spindle cells are epithelial in nature. In some cases, a proportion of the spindle cells are immunoreactive for myoid markers such as actin or myoglobin, but not desmin {83,1442,1834,2341}. Staining for CD34 remarkably highlights the smaller stromal cells between the fascicles of spindle cells as well as some spindle cells.

Ultrastructure

The spindle cells exhibit tonofilaments and desmosomes.

Prognostic factors

This benign lesion does not recur after excision. In the rare examples reported to show malignant change, there has not been recurrence or metastasis {1442}. Such cases focally feature closely packed glands lined by highly atypical cells, but there is no frank invasion beyond the parent tumour.

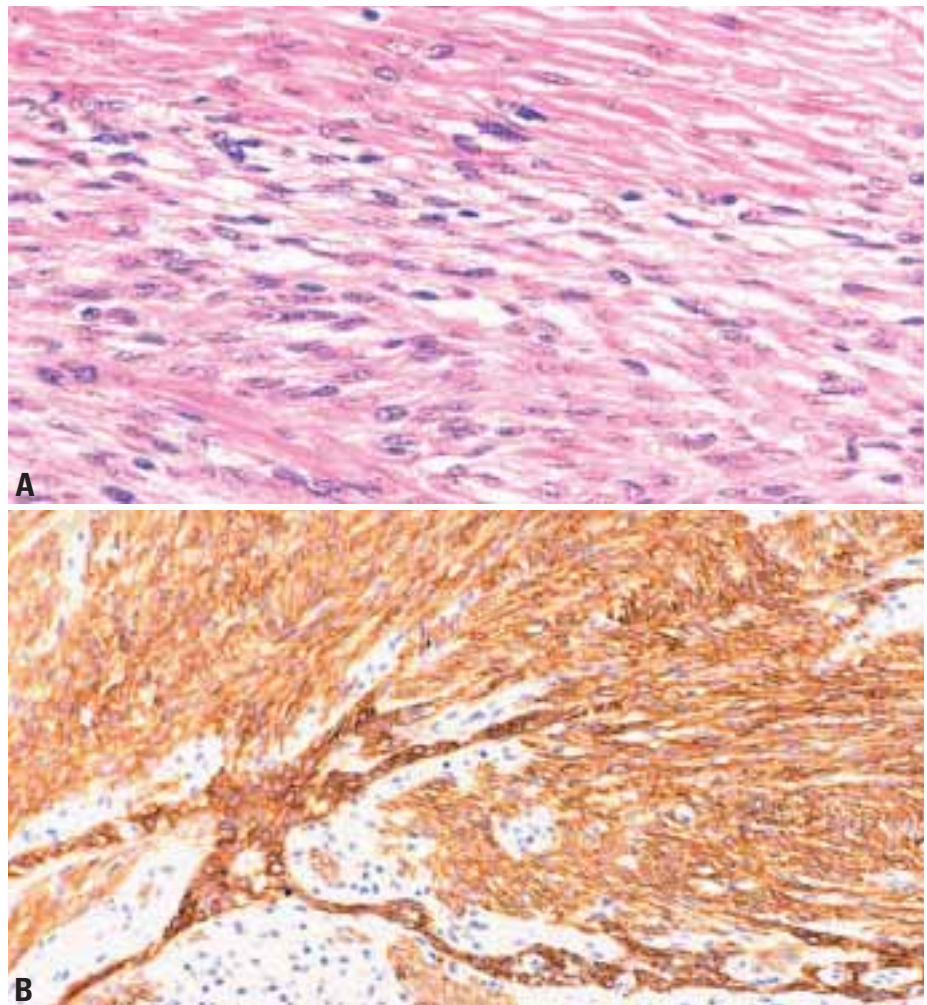


Fig. 9.15 Ectopic hamartomatous thymoma. **A** The spindle cells form compact fascicles. The nuclei are bland-looking, often with pointed ends. Some cells have deeply eosinophilic cytoplasm, suggestive of a myoid phenotype. **B** Immunostaining for cytokeratin highlights both the epithelial strands and the spindle cells. The immunonegative smaller stromal cells in between are strongly positive for CD34 (not shown).

Angiomatoid fibrous histiocytoma

J.C. Fanburg-Smith
P. Dal Cin

Definition

Angiomatoid fibrous histiocytoma (AFH) generally affects children and young adults. It has a partially myoid phenotype and low metastatic potential. This tumour should not be confused with, and is not identical to, aneurysmal fibrous histiocytoma of skin.

ICD-O code 8836/1

Synonym

Angiomatoid malignant fibrous histiocytoma.

Epidemiology

Originally described by Enzinger in 1979 [593], AFH comprises 5% of tumours designated as "malignant fibrous histiocytoma" and approximately 0.3% of all soft tissue tumours. Although AFH has a wide age range from birth [81] to 71 years old [638], it is predominantly a tumour of children and young adults, with a mean age of 20 years. In larger series, there is a slight female predilection [404, 638], whereas other series show a male predominance [593, 1700].

Sites of involvement

The extremities are the most common site for AFH, followed by the trunk and

head and neck. Sixty-six percent of lesions [638] occur in areas where normal lymph nodes may be found, i.e. antecubital fossa, popliteal fossa, axilla, inguinal area, supraclavicular fossa, and anterior and posterior neck.

Clinical features

AFH is mainly a slow-growing tumour of the deep dermis and subcutis and may often simulate a haematoma. Some patients report antecedent trauma to the area; pain is generally not a symptom. Occasional associated systemic signs of fever, anaemia, and weight loss suggest cytokine production by the tumour, similar to haematopoietic tumours such as fibroblastic reticulum cell sarcoma [59], another suggestion of the possible relationship of AFH to this entity. MRI of AFH may reveal fluid-fluid levels, indicating haemorrhage, similar to that seen for aneurysmal bone cyst [1522].

Macroscopy

The median size for AFH is 2.0 centimeters, range 0.7 to 12.0 centimeters [404, 593, 638]. Its firm consistency and circumscribed, tan-grey appearance grossly resembles a lymph node. On cut surface, it is often multinodular with blood-filled cystic spaces and a red-

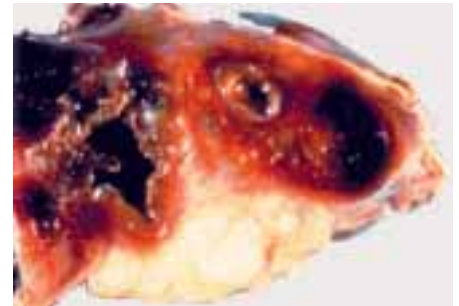


Fig. 9.16 Angiomatoid fibrous histiocytoma. The macroscopic appearance resembles haematoma or haemorrhage within a lymph node.

brown appearance, denoting haemosiderin, occasionally simulating a haematoma or cystic haemorrhage within a lymph node.

Histopathology

The four key morphologic features of AFH may be found in varying proportions: (1) a multinodular proliferation of eosinophilic, histiocytoid or myoid cells, (2) pseudoangiomatoid spaces, (3) a thick fibrous pseudocapsule, and (4) a pericapsular lymphoplasmacytic infiltrate. The latter three features may variably be absent or not apparent on the submitted histologic sections. Always present are the spindled or epithelioid

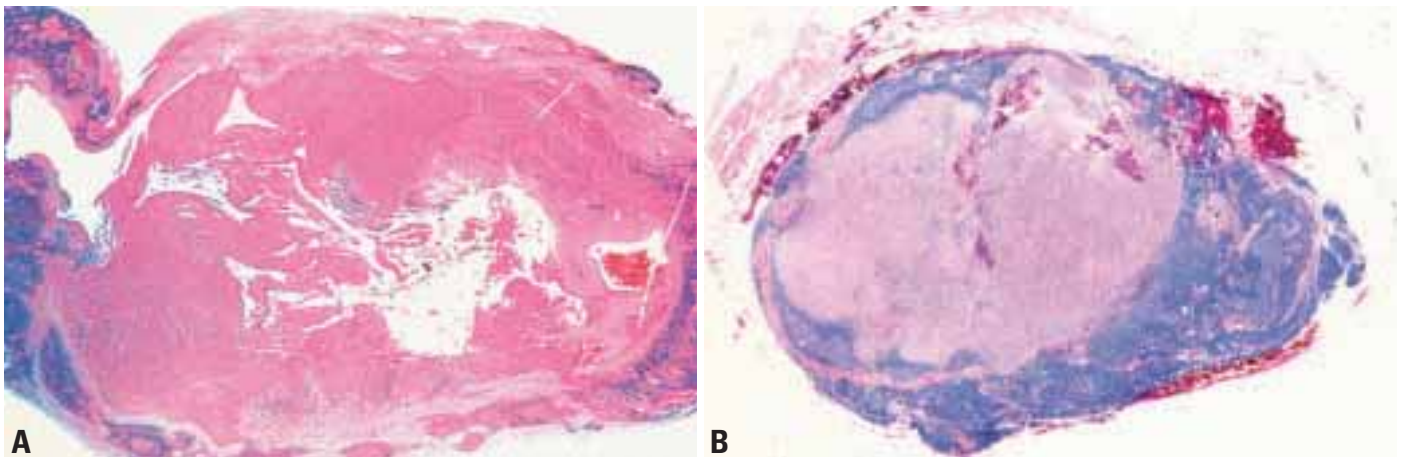


Fig. 9.17 Angiomatoid fibrous histiocytoma. **A** Low magnification microscopic appearance of the tumour shown in Fig. 9.16, showing cystic dilation, partially filled with blood and surrounded by lymphoid tissue. **B** Another example demonstrating typical morphological features: fibrohistiocytic and lymphoid proliferation, angiomatoid blood filled cystic spaces, and pseudocapsule all simulating a tumour within a lymph node.

cells, generally uniform with ovoid vesicular nuclei and often arranged in nodules. The pseudoangiomatoid spaces are not lined by endothelium but rather are cystic spaces within the tumour, filled with blood. The lymphoplasmacytic infiltrate and occasional germinal centre formation make this tumour simulate a lymph node tumour histologically; however, the infiltrate is often outside of the pseudocapsule and subcapsular sinuses or hilar lymphatics of a lymph node are absent in AFH. Cannon-ball-like growth pattern and myxoid change is sometimes observed. Cellular pleomorphism and increased mitotic activity may be identified, particularly in the spindled tumours, but does not correlate with outcome {404}.

Immunophenotype

AFH is positive for desmin in 50% of cases, often also with scattered desmin positive cells within the lymphoid proliferation {403,638,674,898,1971}.

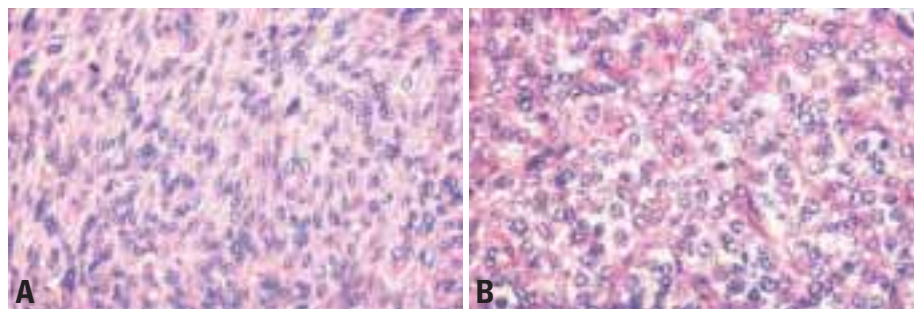


Fig. 9.18 Angiomatoid fibrous histiocytoma. Fibrohistiocytic (myofibroblastic) proliferation with (A) spindled or (B) epithelioid morphology.

Approximately 40% of cases show EMA positivity and many examples show staining for CD68. Yet strong evidence for histiocytic, smooth muscle or skeletal muscle phenotype are absent. Half of the cases may be positive for the nonspecific marker CD99 {638,898}. The tumour cells are uniformly negative for other reticulum cell tumour markers (CD21, CD35), S100 protein, HMB-45, keratins, CD34, and vascular-specific markers (CD31, Factor VIIIrag).

Ultrastructure

Published ultrastructural data have been conflicting and inconclusive with regard to the line of differentiation in tumour cells, perhaps in part due to sampling error.

Genetics

Only one angiomatoid MFH with chromosome aberrations has so far been reported {2222}. Complex rearrangements involving chromosomes 2, 12, 16 and 17, as well as a del(11)(q24) were observed. Further molecular investigation revealed that the *FUS* (a.k.a. *TLS*) gene, mapping to chromosome band 16p11, was fused with the *ATF1* gene, located in band 12q13. The translocation thus generates a chimeric *FUS/ATF1* protein, similar to the *EWS/ATF1* chimeric protein seen in clear cell sarcomas with a t(12;22)(q13;q12).

Prognostic factors

AFH has overall indolent behaviour with 2-11% local recurrences {404, 638} and less than 1% metastases, generally non-fatal to regional lymph nodes {638} and rare deaths due to late distant metastases {403, 404, 593, 1700}. While local recurrence may be higher with infiltrating margins, location on the head and neck, and deep intramuscular location {404}, there are no known clinical, morphological, or genetic factors that predict metastasis. Wide local excision is the treatment of choice for primary tumours {404, 638}.

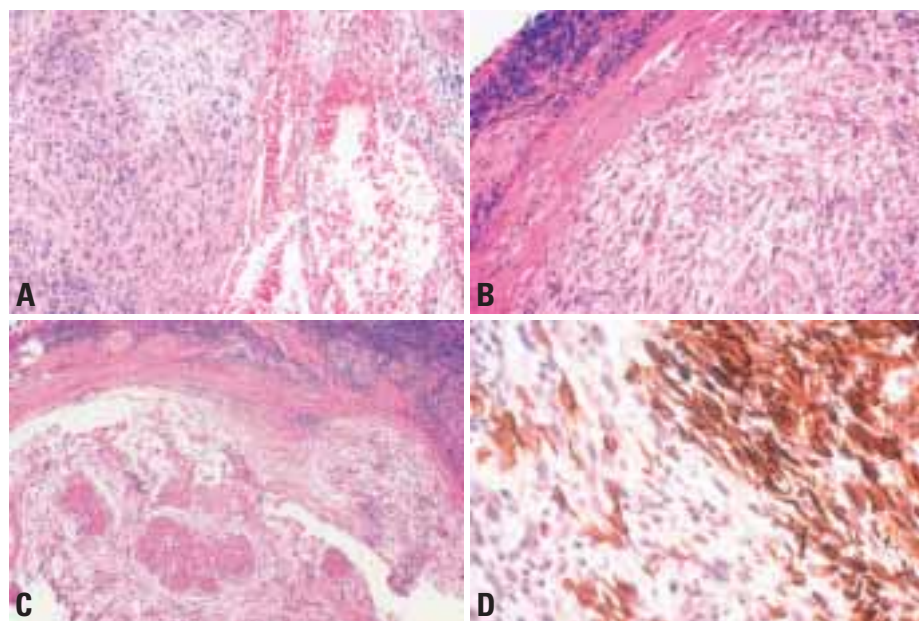


Fig. 9.19 Angiomatoid fibrous histiocytoma. A Pseudoangiomatoid blood-filled cystic spaces without endothelial lining. B Fibrous pseudocapsule surrounds lymphoplasmacytic and fibrohistiocytic (myofibroblastic) components and the absence of subcapsular sinus or hilar lymphatics are evidence against a true lymph node process. C Occasional cannon ball-like growth pattern of myofibroblastic cells with myxoid change. D Desmin immunoreactivity is seen in approximately half of cases.

Ossifying fibromyxoid tumour

B.P. Rubin
G. Stenman

Definition

Ossifying fibromyxoid tumour is a rare neoplasm of uncertain lineage, with cords and trabeculae of ovoid cells embedded in a fibromyxoid matrix, often surrounded by a partial shell of lamellar bone. Occasionally, this lesion may acquire a malignant phenotype.

ICD-O codes

Ossifying fibromyxoid tumour	8842/0
Ossifying fibromyxoid tumour (malignant)	8842/3

Epidemiology

Males (64%) are affected more frequently than females. Lesions tend to occur in adults with patient age ranging from 14-79 years with a median age of 50 years.

Sites of involvement

Approximately 70% of cases arise in the extremities {602}. Other sites of involvement include the trunk, head and neck, oral cavity, mediastinum, and retroperitoneum {602,1513,2111}.

Clinical features

Most patients present with a small, painless, subcutaneous mass, often attached to the underlying tendons, fascia, or skeletal muscle. Lesions are usually of longstanding duration and have been present from 1 to 20 or more years (median 4 years). Radiological studies characteristically, but not invariably reveal a well circumscribed, lobulated mass, with irregular calcifications within the mass, surrounded by an incomplete ring of calcification {602,1873}. Erosion of underlying bone and periosteal reaction has also been noted in some cases {602,1873}.

Macroscopy

Most lesions range from 3-5 cm in greatest dimension with a median size of about 4 cm. Occasional examples are large, measuring up to 17 cm or larger {602}. Ossifying fibromyxoid tumours are well circumscribed, nodular or multinodular, and typically covered by a thick fibrous pseudocapsule with or without a

shell of bone. On cut section, they are white to tan in colour, and either firm, hard, or rubbery in texture.

Histopathology

Ossifying fibromyxoid tumour is composed of lobules of uniform, round to fusiform-shaped cells arranged in nests

and cords, and set in a variably fibromyxoid stroma. Approximately 80% of lesions are surrounded by an incomplete shell of metaplastic (hypocellular) lamellar bone, while the other 20% of cases lack a shell of bone (non-ossifying variant) {602,1444,1894,2273}. The neoplastic cells are monomorphous with round-to-ovoid

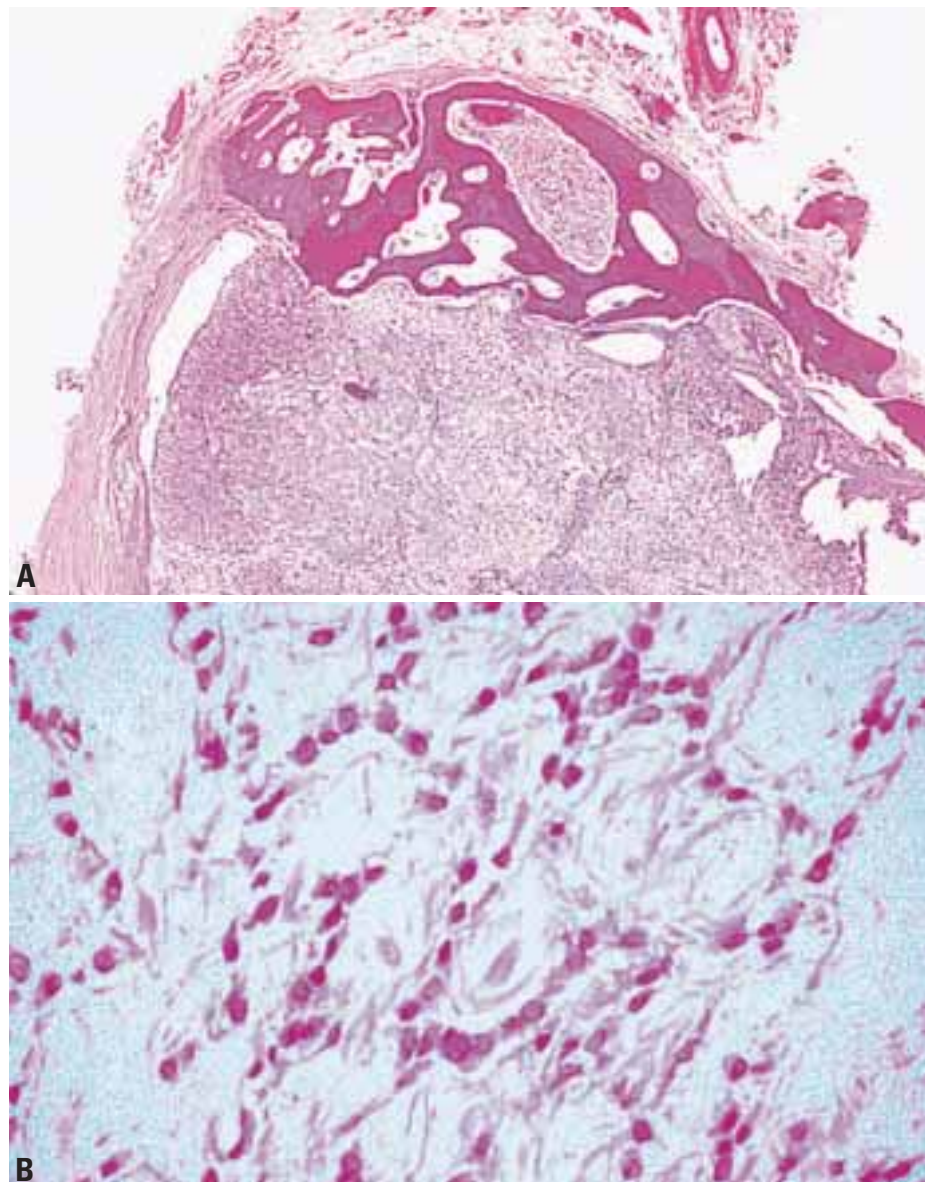


Fig. 9.20 Ossifying fibromyxoid tumour. **A** This lesion is partially surrounded by lamellar bone and partially by a thickened fibrous pseudocapsule. **B** Anastomosing cords of cells set in a myxoid matrix.

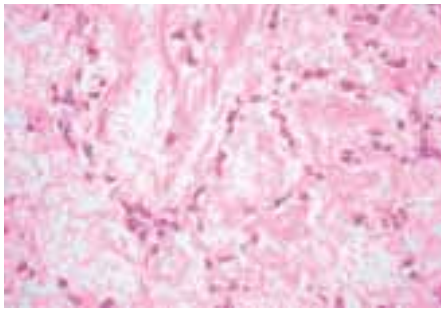


Fig. 9.21 Ossifying fibromyxoid tumour. The cells are monomorphic and have vesicular nuclei with inconspicuous nucleoli, and scant eosinophilic cytoplasm.

nuclei and inconspicuous nucleoli, and a scant amount of eosinophilic cytoplasm. Mitotic activity is usually less than 1 per 10 high power fields. The stroma is quite variable and can be predominantly myxoid (alcian blue positive, hyaluronidase sensitive) or collagenous/hyalinized with a prominent vasculature which can exhibit perivascular hyalinization. Calcifications and/or nodules of metaplastic cartilage are occasionally identified.

Rare examples of ossifying fibromyxoid tumour are hypercellular and/or have increased numbers of mitotic figures and deposition of tumour osteoid by neoplastic cells randomly, or more frequently, within the centre of the lesions. One such case showed features reminiscent of osteosarcoma {602}. These lesions have been termed "atypical" or "malignant" (for those tumours that metastasise) {1104}. Furthermore, these "atypical" or "malignant" ossifying fibromyxoid tumours tend to have a much less complete shell of bone than conventional examples.

Immunophenotype

Ossifying fibromyxoid tumours (including atypical and malignant examples) are typically positive for vimentin and S100 protein (70%), often show desmin positivity and may also express Leu-7, neuron-specific enolase, glial fibrillary acidic protein and smooth muscle actin (rare)

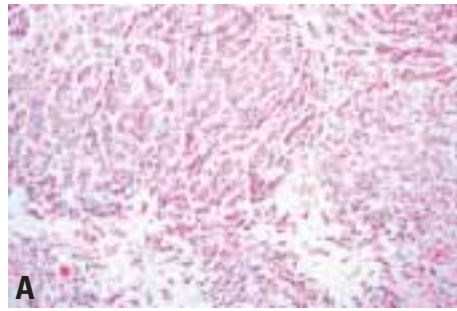
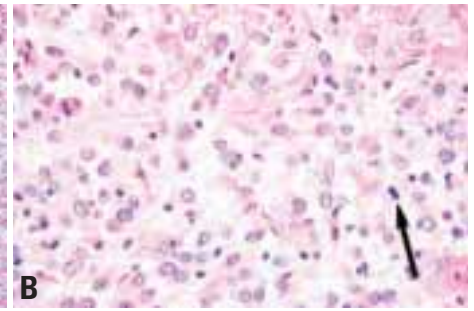


Fig. 9.22 Atypical / malignant ossifying fibromyxoid tumour. **A** Cellular areas and centrally placed osteoid. **B** Cells have enlarged nuclei and more prominent, sometimes multiple, nucleoli. Note the mitotic activity (arrow).



{602, 669, 1104, 1444, 1894, 2273, 2319}. Rare cases show focal keratin positivity.

Ultrastructure

The cytoplasm contains prominent rough endoplasmic reticulum, often with cisternal dilatations, moderate numbers of mitochondria, and numerous microfilaments, often clustered in the perinuclear area {533, 669, 1444}. Ribosome-lamellar complexes have also been described {669}. Many cells have a partial reduplicated external lamina, and occasional cells have complex, sometimes interdigitating cell processes.

Genetics

A single case of ossifying fibromyxoid tumour has been analysed cytogenetically {2003}. The tumour had a hypodiploid karyotype distinguished by a der(6;14)(p10;q10) and an add(12)(q24).

Prognostic factors

Follow-up data is available in 41 cases of ossifying fibromyxoid tumour from the largest series {602}. Recurrences were noted in 11 cases (27%), sometimes multiple. One patient had a presumed metastasis to the contralateral thigh (in contrast to a second primary lesion) 20 years after excision of the primary {602}. The histological and clinical features of

the majority of the recurrent tumours were identical to the non-recurrent tumours. However, increased mitotic activity (8-10 mitotic figures per 10 high power fields) and increased cellularity were noted in some of the recurrent lesions. These latter lesions would probably be regarded as "atypical" or "malignant" ossifying fibromyxoid tumours by some. Clinical follow-up in the 3 cases reported as "atypical" or "malignant" with significant follow-up, revealed local recurrence in one case 2 years after excision of the primary, and pulmonary metastasis at the time of presentation followed by a local recurrence and additional pulmonary metastasis 25 months later in the other {1104}.



Fig. 9.23 Ossifying fibromyxoid tumours typically show diffuse immunoreactivity for S100 protein.

Mixed tumour / Myoepithelioma / Parachordoma

S.E. Kilpatrick
J. Limon

Definition

Mixed tumours are well circumscribed lesions displaying epithelial and / or myoepithelial elements in varying proportions, within a hyalinized to chondromyxoid stroma. Those tumours, comprised mostly of myoepithelial cells, closely resembling those observed in pleomorphic adenoma, and lacking obvious ductal differentiation, are designated myoepitheliomas. Parachordomas closely resemble mixed tumours / myoepitheliomas and are best considered within this spectrum.

ICD-O codes

Mixed tumour, not otherwise specified	8940/1
Mixed tumour, malignant, not otherwise specified	8940/3
Myoepithelioma	8982/1
Parachordoma	9373/1

Synonym

Ectomesenchymal chondromyxoid tumour.

Epidemiology

The actual incidence of this group of tumours is difficult to estimate, as they have only recently been adequately characterized. Mixed tumours/myoepitheliomas and parachordomas are usually found in adults, average age 35 years {694,1104}. A significant number of patients, possibly up to 20%, are children less than 10 years of age. There may be a slight male predominance but data are limited.

Sites of involvement

The vast majority of cases arise in the subcutaneous or deep subfascial soft tissues of the extremities (upper > lower extremities). Less commonly, localization within the head and neck and trunk regions is observed. Rare reports have documented mixed tumours arising from bone, all involving the extremities {475}.

Clinical features

Most patients present with superficial to subfascial, painless swellings, ranging

from a few weeks to several years duration. Localized pain is rarely reported.

Histopathology

Histologically, mixed tumours of soft tissue show the same morphologic spec

trum observed in their salivary gland counterparts. Varying proportions of uniform-appearing, epithelioid cells with eosinophilic to clear cytoplasm, arranged in nests, cords, and ductules, and/or spindled cells, are embedded in a

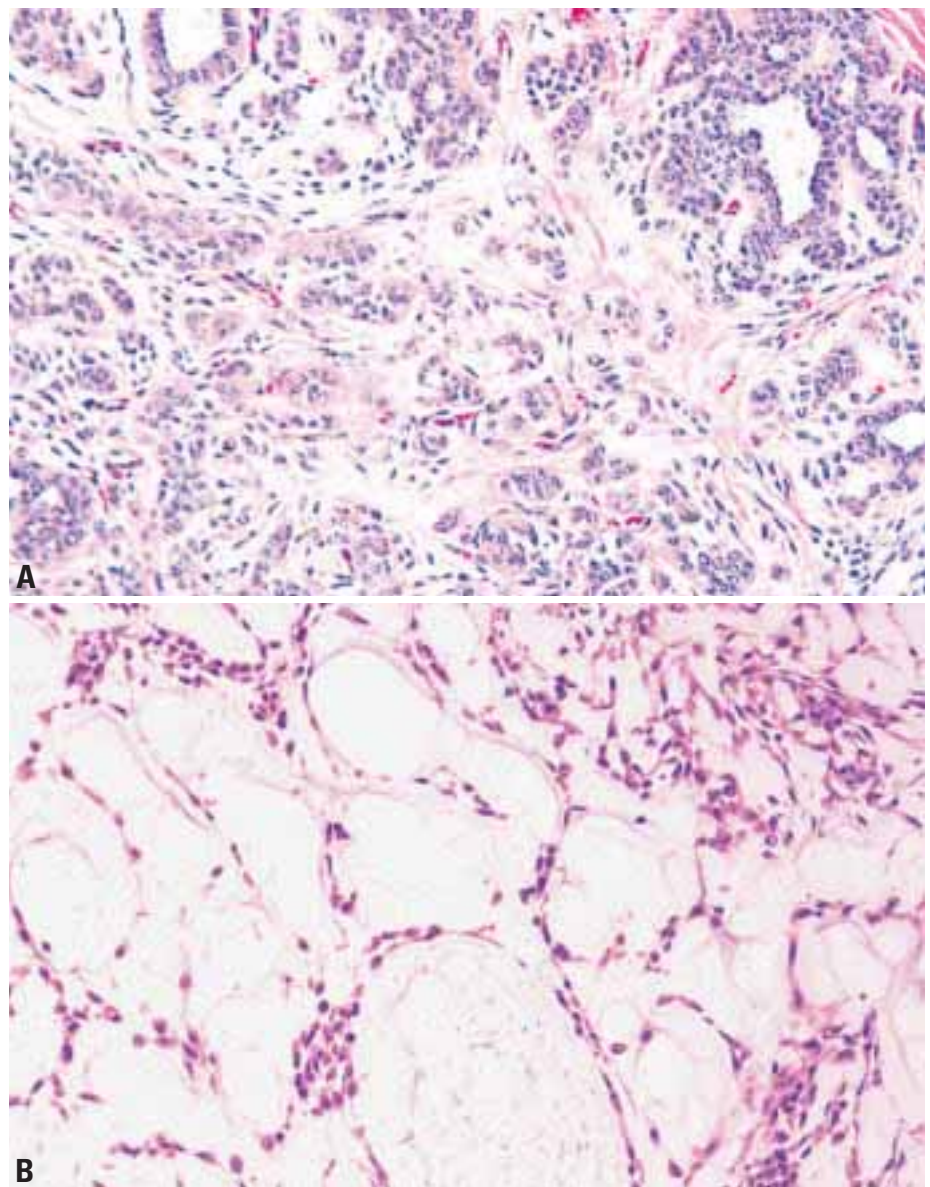


Fig. 9.24 Myoepithelioma / mixed tumour. **A** Epithelioid cells arranged in nests, ductules, and glandular patterns within a partially myxoid stroma. **B** Many cases have a reticular growth pattern, reminiscent of myxoid chondrosarcoma.

hyalinized to chondromyxoid matrix {1104, 1439}. Divergent differentiation, including squamous, adipocytic, and bone and cartilaginous metaplasia, may be observed. From a strict histologic perspective, myoepitheliomas differ from mixed tumours in that they typically lack a definite ductal component. Additionally, the myoepithelial cells range from plasmacytoid forms to spindle cells. Intracytoplasmic hyaline inclusions, a feature previously described in rare cases of chondroid syringoma of the extremities, are rarely observed, sometimes imparting a "rhabdoid" like appearance {654,1104}. Parachordomas closely resemble mixed tumours with the exception that cytoplasmic vacuolation may be a prominent feature in the former {420,694}. Mitotic activity tends to be scant, <2 mitoses per 10 high power fields and nuclear pleomorphism is generally minimal. Similar to salivary gland lesions, dedifferentiation into frank carcinoma or sarcoma is seen in occasional cases.

Immunophenotype

Despite a broad morphologic spectrum, greater than 95% of cases express cytokeratin, vimentin, and S100 protein {1104,1439}. Less consistently, positivity for calponin, smooth muscle actin, glial fibrillary acidic protein, desmin, and epithelial membrane antigen are observed.

Genetics

Three cases with clonal aberrations have been published {694,1669,2114}. Two tumours had a hypodiploid and one a hyperdiploid modal chromosome number. Loss of material from 17p was detected in all three cases.

Prognostic factors

The majority of mixed tumours / myoepitheliomas / parachordomas behave in a benign fashion. However, a minority may locally recur and metastasise, resulting in death {1104}. At present, there are no morphological features reliably predictive of prognosis, other than those few lesions which show frankly malignant histological features.

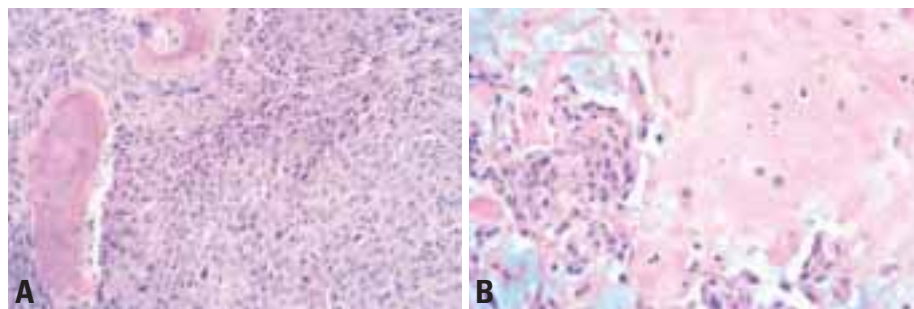


Fig. 9.25 Mixed tumour. **A** Osseous metaplasia within a mixed tumour dominated by myoepithelial cells. **B** Lobules of immature hyaline cartilage adjacent to nests of myoepithelial cells.

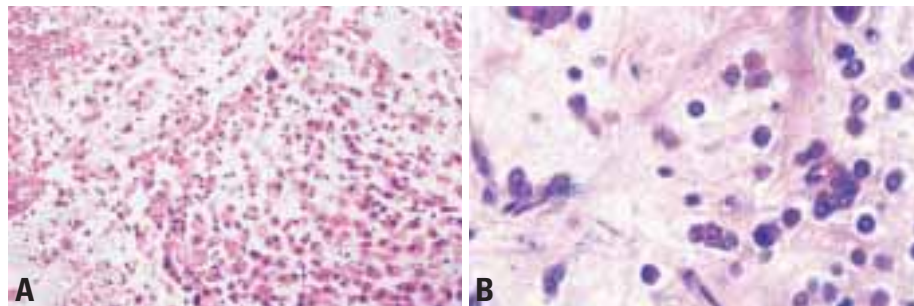


Fig. 9.26 Mixed tumour. **A** Parachordomas are often dominated by large, variably vacuolated eosinophilic epithelioid cells. **B** Rarely, cells may exhibit "rhabdoid" features and intracytoplasmic hyaline inclusions.

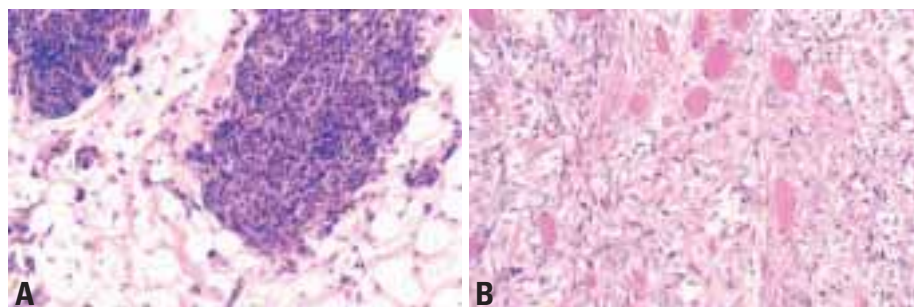


Fig. 9.27 Myoepithelioma. **A** In this case, monomorphic spindle-shaped myoepithelial cells lie adjacent to an area with variable adipocytic differentiation. **B** This lesion from the thigh shows features of carcinoma arising in the context of a myoepithelioma / mixed tumour. Note the marked atypia of the epithelioid cells.

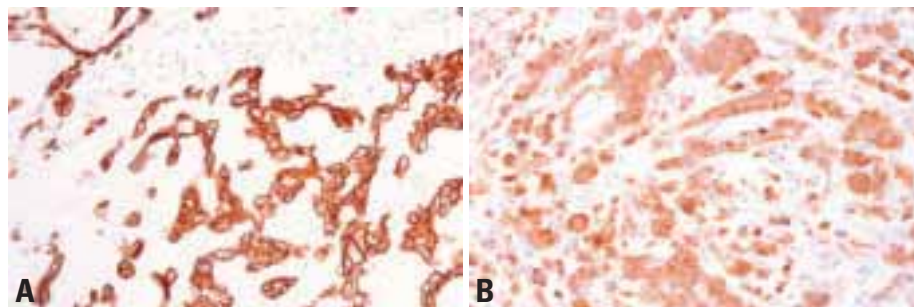


Fig. 9.28 Myoepithelioma. **A** Almost all cases show at least some immunopositivity for keratin, in this case AE1/AE3. Fewer cases stain for epithelial membrane antigen. **B** Most cases are also immunopositive for S100 protein.

Synovial sarcoma

C. Fisher
D.R.H. de Bruijn
A. Geurts van Kessel

Synovial sarcoma (SS) is a morphologically, clinically and genetically distinct entity, that may occur at any site. It does not arise from or differentiate toward synovium, which, unlike SS, lacks epithelial differentiation and has different histochemistry. No origin from or continuity with, pre-existing epithelium has ever been identified. Because of its epithelial features, it has been proposed that SS be renamed carcinosarcoma or spindle cell carcinoma of soft tissue [1451]. However, the term SS is generally recognized and has proven useful.

Definition

Synovial sarcoma is a mesenchymal spindle cell tumour which displays variable epithelial differentiation, including glandular formation and has a specific chromosomal translocation $t(X;18)(p11;q11)$.

ICD-O codes

Synovial sarcoma	9040/3
Synovial sarcoma, spindle cell	9041/3
Synovial sarcoma, biphasic	9043/3

Synonyms

Older synonyms such as tendosynovial sarcoma, synovial cell sarcoma, malignant synovioma, and synovioblastic sarcoma should be abandoned.

Epidemiology

SS accounts for 5 to 10% of soft tissue sarcomas [1168]. They are reported from birth to 89 years but occur mainly in young adults and more commonly in males; 90% of cases occur before 50, and most between 15 and 35 years.

Sites of involvement

SS is unrelated to synovium and <5% originate within a joint or bursa. Over 80% arise in deep soft tissue of extremities, especially around the knee and the tumour frequently arises adjacent to joints or tendon sheaths. Around 5% arise in the head and neck region; however, any site can be affected [79,668, 690,1018].

Clinical features

There is usually a mass with or without pain. In specific sites local symptoms, e.g. dysphagia, relate to effects of a mass. Growth is often slow, averaging 2-4 years, and 20-year histories are known. Some tumours have radiologically detectable irregular calcification that is occasionally massive.

Aetiology

There are no specific predisposing factors. One example was associated with a metal implant used in hip replacement [1215], and another with previous therapeutic irradiation for Hodgkin disease [2171]. SS has a chromosomal translocation that is presumably relevant in pathogenesis (see below).

Macroscopy

The typical SS is 3-10 cm in diameter, and circumscribed (when slowly growing) or infiltrative. The tumour is tan or grey, and soft when lacking fibrous stroma. It is frequently multinodular, and can be multicystic. Necrosis is seen in poorly differentiated (PD) SS.

Histopathology

Histologically, SS is biphasic or monophasic. *Biphasic SS* has epithelial and spindle cell components, in varying proportions. The epithelial cells have ovoid nuclei and abundant cytoplasm. They form glands with lumina (containing epithelial mucin) or papillary structures with one or (rarely) more layers of uniform

cells. The glandular component can predominate [1312] with large closely packed glands and a scanty spindle component that can be overlooked, allowing misinterpretation as adenocarcinoma. The epithelial component can also form solid cords, nests or rounded clusters. Squamous metaplasia, sometimes with keratinization, occurs in about 1% of cases [1474]. The spindled (not "stromal") tumour cells are uniform and relatively small, with ovoid, pale-staining nuclei and inconspicuous nucleoli. Cytoplasm is sparse and cell borders are indistinct, so that nuclei appear to overlap. Mitoses can be scarce, except in poorly differentiated SS. The spindle cell component often occurs alone as *monophasic SS*. Typically

Table 9.01

Unusual Sites of Occurrence of Synovial Sarcoma.

Head and Neck	Intra-abdominal
Orofacial	Mesentery
Tongue	Retroperitoneum
Tonsil	Intrathoracic
Larynx	Mediastinum
Trachea	Pleura
Parapharynx	Lung
Abdominal wall	Heart
Vulva	Oesophagus
Penis	Intraneural
Kidney	Intra-osseous
Prostate	Intra-articular
Skin	Intracranial
Intravascular	Third ventricle

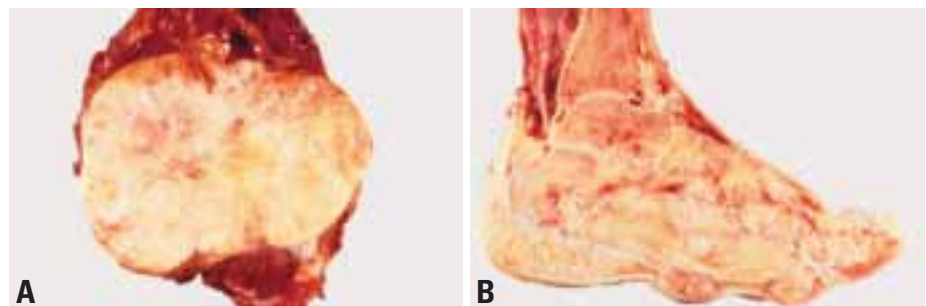


Fig. 9.29 **A** Biphasic synovial sarcoma of thigh showing a white-tan, firm cut surface. **B** Surgical specimen of a monophasic synovial sarcoma of the foot, showing a destructive lesion with a white-tan cut surface.

there are densely cellular sheets or vague fascicles, with occasional nuclear palisading. Many tumours display, at least focally, a prominent haemangiopericytoma-like vascular pattern. Extensive sampling can sometimes reveal an epithelial component but this is not necessary for diagnosis.

Stromal collagen is usually wiry and scanty but some tumours have foci of dense fibrosis, especially after irradiation. Myxoid change is usually focal (and rarely diffuse and predominant {1167}), with alternating hypocellular and more cellular areas, and microcyst formation. Mast cells can be abundant.

Purely glandular monophasic SS theoretically exists but is indistinguishable from adenocarcinoma without cytogenetics. SS composed of plump epithelioid cells has sometimes been termed *monophasic epithelial SS*, but examples with rhabdoid cells are included with PD SS.

Calcifying SS. About one third of SS show focal tumoural calcification, with or without ossification. When extensive the prognosis is improved {2191}. Some have antecedent trauma. Most are biphasic {2191}, with calcification in glandular lumina, but they can be monophasic with a deceptively bland or hypocellular spindle component. In ossifying SS, the osteoid has a lace-like pattern mimicking osteosarcoma, and the bone is lamellar and trabecular {1456}. Separately, metaplastic bone or cartilage can occur in the stroma.

Poorly differentiated SS. Areas with high cellularity, numerous mitoses and often necrosis are present in many SS but in some tumours (perhaps 20% of all SS) these predominate {703,2170}. There are typically sheets of darkly staining ovoid or rounded cells like those in other small

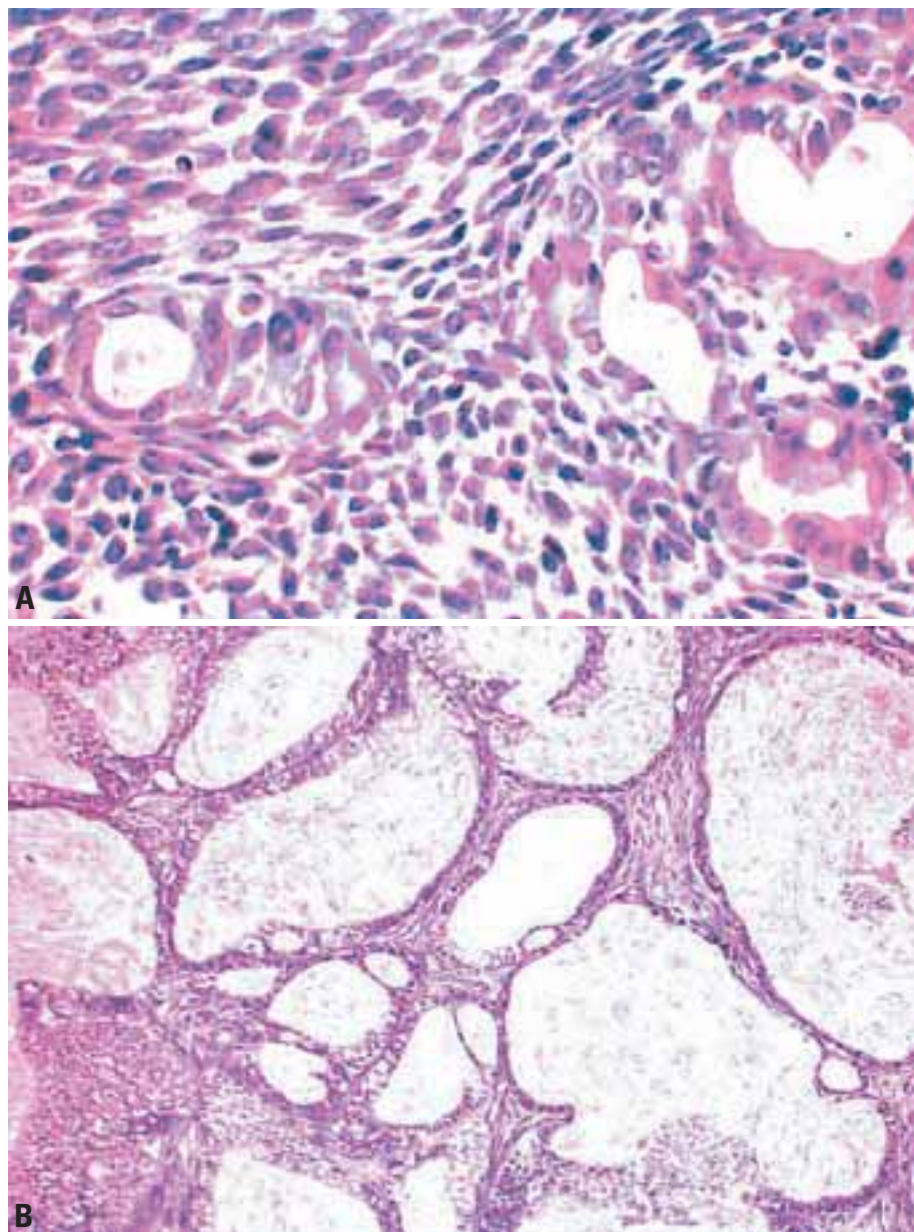


Fig. 9.30 **A** Biphasic synovial sarcoma with glandular and spindle cell component. **B** Predominantly glandular synovial sarcoma. Variably-sized mucin-secreting glands with a scanty spindle cell component.

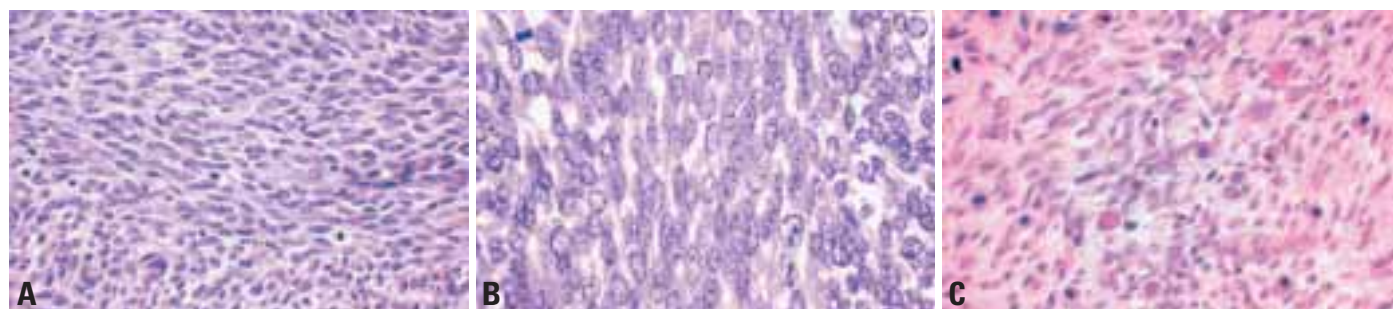


Fig. 9.31 Monophasic synovial sarcoma. **A** Typical appearance with fascicles and sheets of uniform, relatively small ovoid neoplastic cells. **B** High power magnification of the spindle component. **C** Mast cells may be abundant in the spindle cell component.

round cell tumours, especially PNET. The cells are sometimes larger with more cytoplasm, and can appear rhabdoid. Rarely, the rather uniform spindle cells of MSS can be somewhat pleomorphic. PDSS have the same immunophenotype and genetic abnormalities as regular SS {2170}.

Immunophenotype

About 90% of all SS express cytokeratins (CK), in the epithelial component and in rare cells in the spindle cell component. In MSS, CK-positive cells are seen singly, or in cords, nests or sheets; this can be focal and not present in every block. Several CK subtypes are expressed including cytokeratins 7 and 19 {1443}; these are absent from malignant peripheral nerve sheath tumour {1977} and Ewing Sarcoma / PNET {1303}, which is diagnostically useful. Epithelial membrane antigen (EMA) is expressed more often and more widely than CK, especially in the poorly-differentiated subtype. It outlines glandular lumina, and slit-like spaces in solid epithelial areas, and the surface of single cells or small nests in MSS. Some cases are EMA+ but CK-, or vice versa so that both markers should be used.

S100 protein may be detectable (in nuclei and cytoplasm) in 30% of synovial sarcomas including MSS {854}. CD99 is positive in 62% of SS, in the cytoplasm of epithelial cells and with membrane staining on spindle cells, mimicking that in ES/PNET {492}. BCL2 protein is diffusely expressed in all SS, especially in spindle cells {2060}. However, CD34 is usually negative. Amongst muscle markers, calponin is found in most SS. Desmin is absent, but occasionally in MSS there is focal positivity for muscle specific or smooth muscle actin. Vimentin is present in the spindle cells of SS.

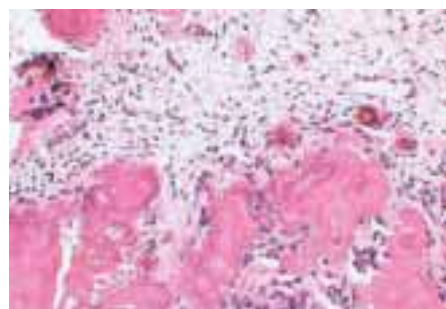


Fig. 9.32 Ossifying synovial sarcoma showing irregular bone formation within the tumour and scant neoplastic spindle cells.

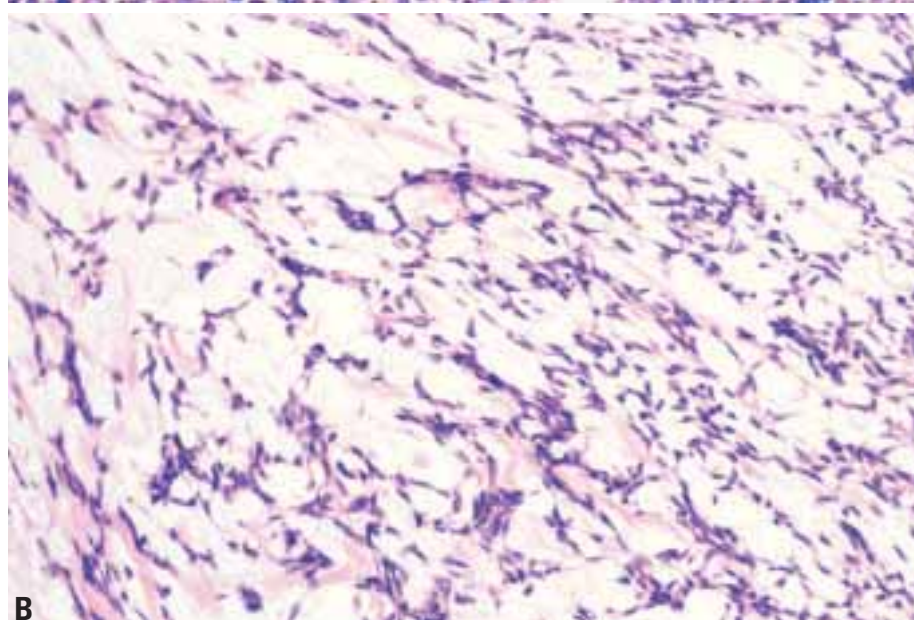
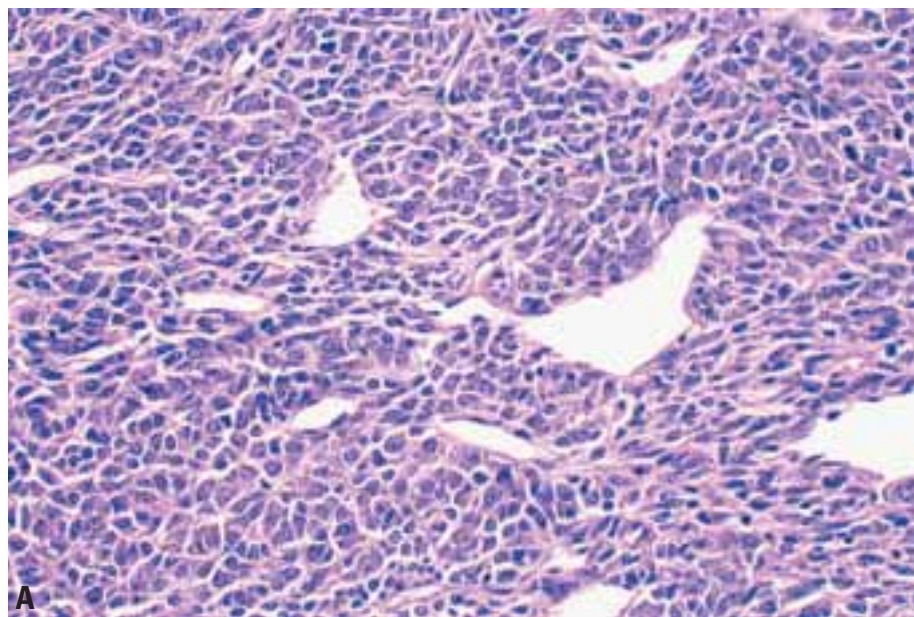


Fig. 9.33 **A** A haemangiopericytomatous vascular pattern is seen in many monophasic synovial sarcomas. **B** In myxoid synovial sarcoma spindle-shaped tumour cells are widely dispersed in a myxoid stroma.

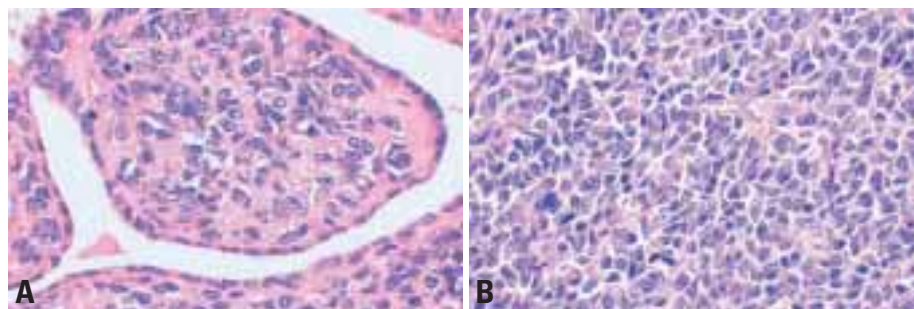


Fig. 9.34 Poorly differentiated **(A)** biphasic and **(B)** monophasic synovial sarcoma.

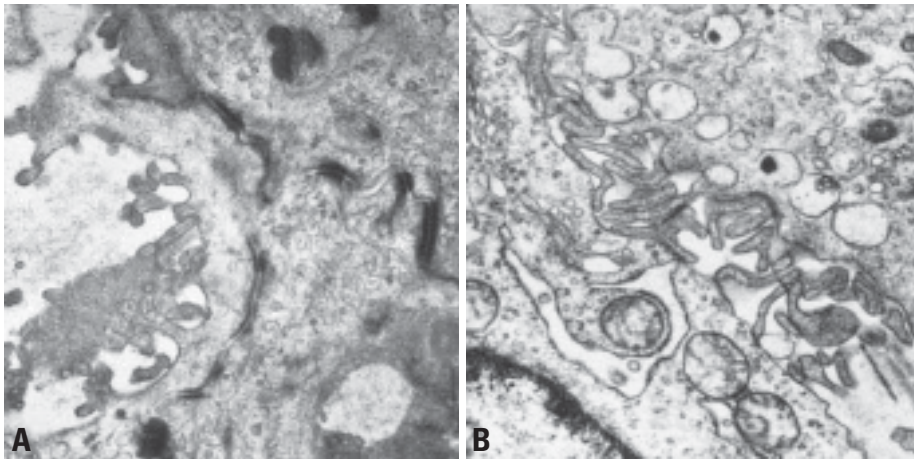


Fig. 9.35 **A** Electron microscopy of a biphasic synovial sarcoma showing a well defined glandular-like lumen with few projecting microvilli, amorphous intraluminal material and desmosomal junctional complexes. **B** Monophasic synovial sarcoma with abortive lumina and projecting microvilli.

Ultrastructure

The epithelial component is similar to adenocarcinoma {665}. External lamina encloses groups of cells containing intermediate filaments including tonofilaments. Cells are joined by a terminal bar complex and have surface microvilli protruding into the glandular lumen. In MSS, the cells are featureless and rarely have prominent RER indicative of fibroblasts. There are very occasional intercellular gaps, into which protrude short or long processes. Short segments of external lamina associated with single cells can

rarely be found. Transitions between the spindle and the epithelial component are not seen. Calcifying examples show intramitochondrial needle-like calcifications {2280}.

Genetics

Cytogenetics

The t(X;18)(p11;q11) is the cytogenetic hallmark of synovial sarcoma, being present in more than 90% of the 150 cases that have been reported {1477}. Variant, more complex translocations have been described. In one-third of the

tumours it is the sole aberration, whereas the others also have secondary changes, in particular -3, +7, +8, and +12.

Molecular genetics

The genes affected by the t(X;18) have been isolated: *SS18* (a.k.a. *SYT* or *SSX7*), from chromosome 18, and *SSX1*, *SSX2* and *SSX4* from the X chromosome {360, 408,471,472,1966}. Several studies have indicated that the t(X;18) translocation arises exclusively in synovial sarcomas. FISH and (real-time) RT-PCR have been employed widely for the rapid diagnosis of synovial sarcoma {197,473, 973,1004, 1570,1784,1942}. Of at least 350 synovial sarcomas analysed for the presence of *SS18/SSX* fusions, two-thirds showed an *SS18/SSX1* fusion, one-third an *SS18/SSX2* fusion and three separate cases an *SS18/SSX4* fusion {543,543a, 1855}.

The human *SS18* gene is expressed ubiquitously {466,469} and codes for a 55 kDa protein (418 amino acids). The *SSX* gene family encompasses at least five members, encoding 188 amino acid proteins with high sequence homologies. In most *SS18/SSX* fusion proteins identified, the C-terminal 8 amino acids of *SS18* are replaced by the last 78 amino acids of *SSX*. The consequence of this is that the QPGY domain of *SS18* is interrupted and that the KRAB domain of *SSX*

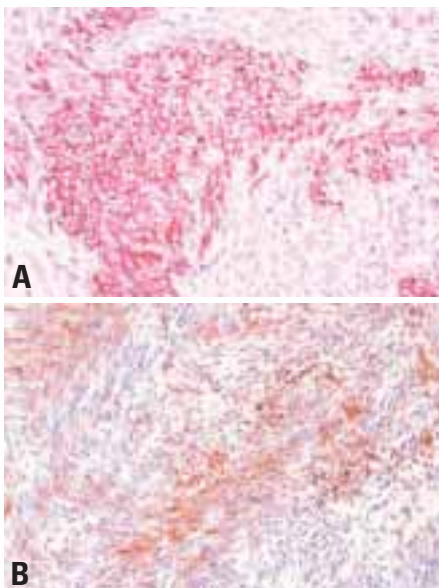


Fig. 9.36 Synovial sarcoma. **A** Cytokeratin positivity in a case of monophasic synovial sarcoma. **B** EMA is a more sensitive immunohistochemical marker than keratin in monophasic and poorly differentiated lesions.

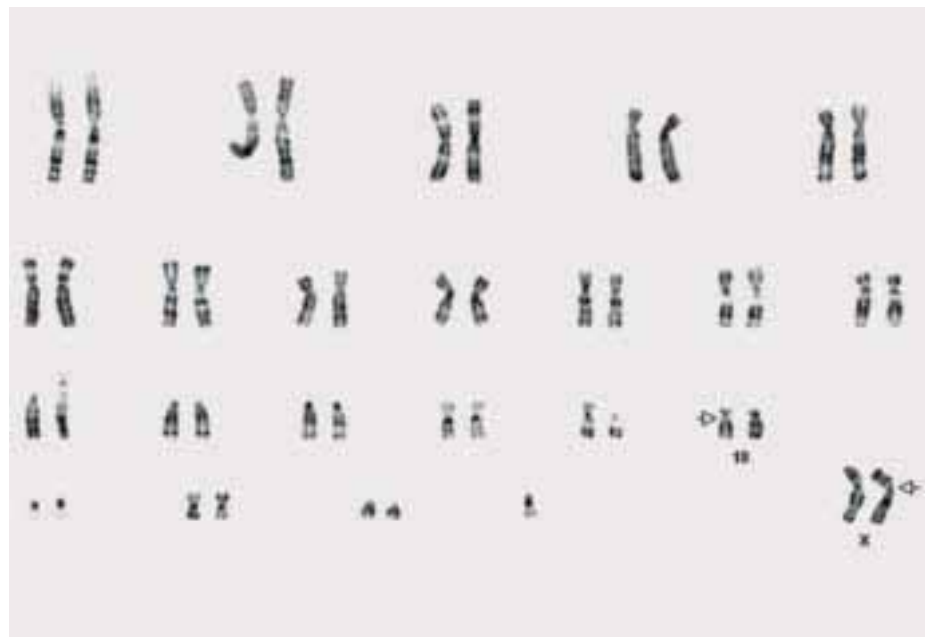


Fig. 9.37 Karyogram showing the t(X;18)(p11;q11) translocation characteristic of synovial sarcoma. Arrows indicate breakpoints.

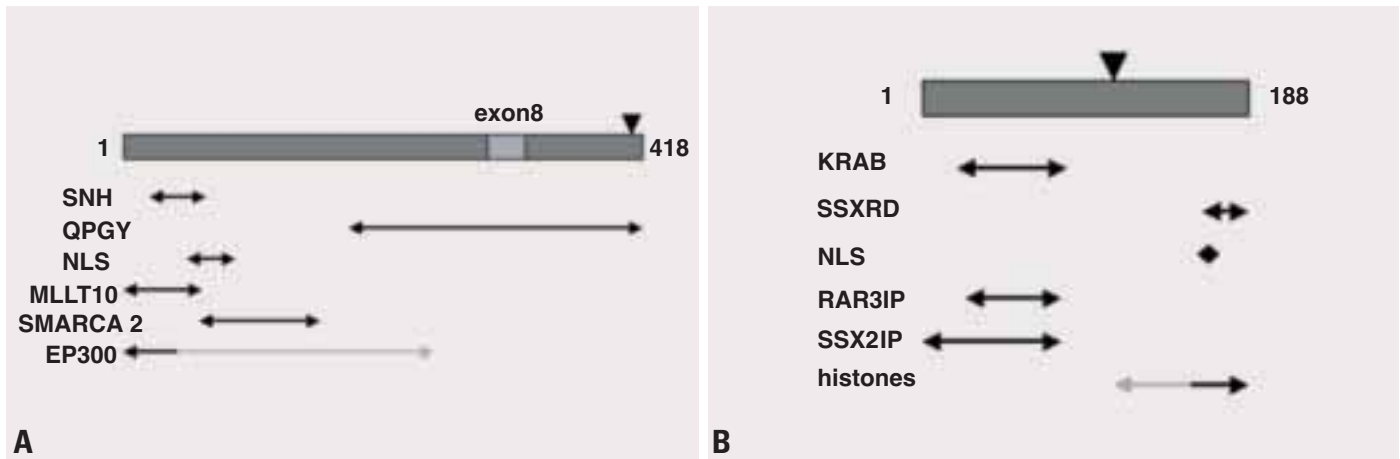


Fig. 9.38 **A** Schematic representation of the SS18 protein which is affected by the t(X;18) translocation. Marked as doubleheaded arrows are the SNH and QPGY domains, as well as the domain responsible for nuclear localization (NLS). Also marked as doubleheaded arrows are the SS18 domains which are responsible for the interactions with MLLT10, SMARCA2 and EP300. Additionally, the most frequent breakpoint in synovial sarcoma (arrowhead) and the the alternatively spliced exon 8 are indicated. **B** Schematic representation of an SSX protein. Marked as doubleheaded arrows are the KRAB and SSX repression domain (SSXR), as well as the nuclear localization signal (NLS). Also marked as doubleheaded arrows are the domains which are responsible for the interactions with RAB3IP, SSX2IP and core-histones. The arrowhead denotes the most frequent breakpoint in synovial sarcoma.

is lost in the fusion protein. Since the other interaction domains of SS18 are retained, the SS18-SSX protein may still interact with the SWI/SNF complex and EP300. Several lines of evidence have indicated that interruption of the SS18 QPGY domain may lead to a loss of function for this domain [252,2106]. This loss may also be caused by aberrant folding through the addition of SSX sequences and/or through aberrant targeting of the whole complex [467,468]. Such aberrant targeting may lead to SWI/SNF mediated chromatin changes in regions which are normally silenced by PcG complexes.

Prognostic factors

Up to 50% of SS recur, usually within 2 years, but sometimes up to 30 years after diagnosis [2242]. Some 40% metastasise, commonly to lungs and bone and also regional lymph nodes. Adequate local excision with postoperative radiotherapy can control local recurrence. 5 year survival is 36-76%, and 10 year survival is 20-63% [2242]. The best outcomes are in childhood patients, in tumours which are <5 cm in diameter, have <10 mitoses / 10 hpf and no necrosis, and when the tumour is eradicated locally [1245,1958,2010]. Prognosis

does not differ between monophasic and biphasic tumours, or in relation to immunophenotype. However, cases with the *SS18/SSX2* variant gene, which is mostly found in MSS, have a better prognosis [71,1077,1569]. PDSS is aggressive, and metastasises in a high percentage of cases. The presence of rhabdoid cells or of more than 50% necrosis, are adverse prognostic factors; in one series, 50% died with a mean survival of 33 months [2171]. The calcifying variant fares better with survival of 83% after five years, and 66% after 10 years [2191].

Epithelioid sarcoma

L. Guillou
Y. Kaneko

Definition

A distinctive sarcoma of unknown lineage showing predominantly epithelioid cytomorphology, affecting mainly adolescents and young adults. This tumour may be misdiagnosed as a benign lesion, especially as a benign granulomatous process.

ICD-O code 8804/3

Epidemiology

Epithelioid sarcoma (ES) was first recognized as a distinctive entity in 1970 by Enzinger [592]. It occurs in young adults mainly between 10 and 39 years of age (median: 26 years) [336]. Male patients

outnumber females by about 2:1 [336,1723], especially in the second through fifth decades of life.

Sites of involvement

The flexor surface of the fingers, hand, wrist, and forearm are most commonly involved, followed by knee and lower leg, proximal extremities, ankle, feet and toes [336]. The trunk (including genital areas) and head and neck regions are seldom involved by classical epithelioid sarcoma.

Clinical features

When superficially located, ES usually presents as firm, slowly growing painless nodules or plaque-like lesions, solitary or

multiple. Ulceration of the skin may occur. Deep-seated lesions are often attached to tendons, tendon sheaths, and / or aponeuroses.

Aetiology

Unknown. A history of trauma is reported in 20% [336] to 25% [1723] of cases.

Macroscopy

In its classical «distal» form, ES usually presents as small, indurated, ill defined, dermal and/or subcutaneous nodules, or larger, variably necrotic masses involving tendons and/or fascia. The cut surface shows a whitish lesion with often a yellow to brown centre due to necrotic and/or haemorrhagic changes. The size of the superficial nodules varies from a few millimeters to 5 cm; deep-seated tumours tend to be larger (up to 15 cm) [336].

Histopathology

The conventional «distal» form of ES shows a characteristic nodular growth pattern and is composed of a mixed proliferation of eosinophilic epithelioid and spindle cells exhibiting slight nuclear atypia, vesicular nuclei and small nucleoli. Transition between the two cell types is gradual and intercellular collagen deposition usually marked. Frequently, tumour nodules undergo central necrosis resulting in a pseudogranulomatous appearance, simulating a benign necrobiotic process such as a rheumatoid nodule or granuloma annulare. Deep-seated and fascial-based tumours often form scalloped or garland-like structures admixed with areas of necrosis [336]. Pseudoangiosarcomatous features due to cell disaggregation, dystrophic calcifications and bone formation (10-20% of cases), and accompanying chronic inflammation are possible additional features [336]. Perineural and perivascular infiltration are commonly seen. The number of mitoses is usually low, often less than 5 per 10 hpf. A «fibroma-like» variant of ES has been described and shows a predominantly spindle cell proliferation with minimal cytological atypia set in an

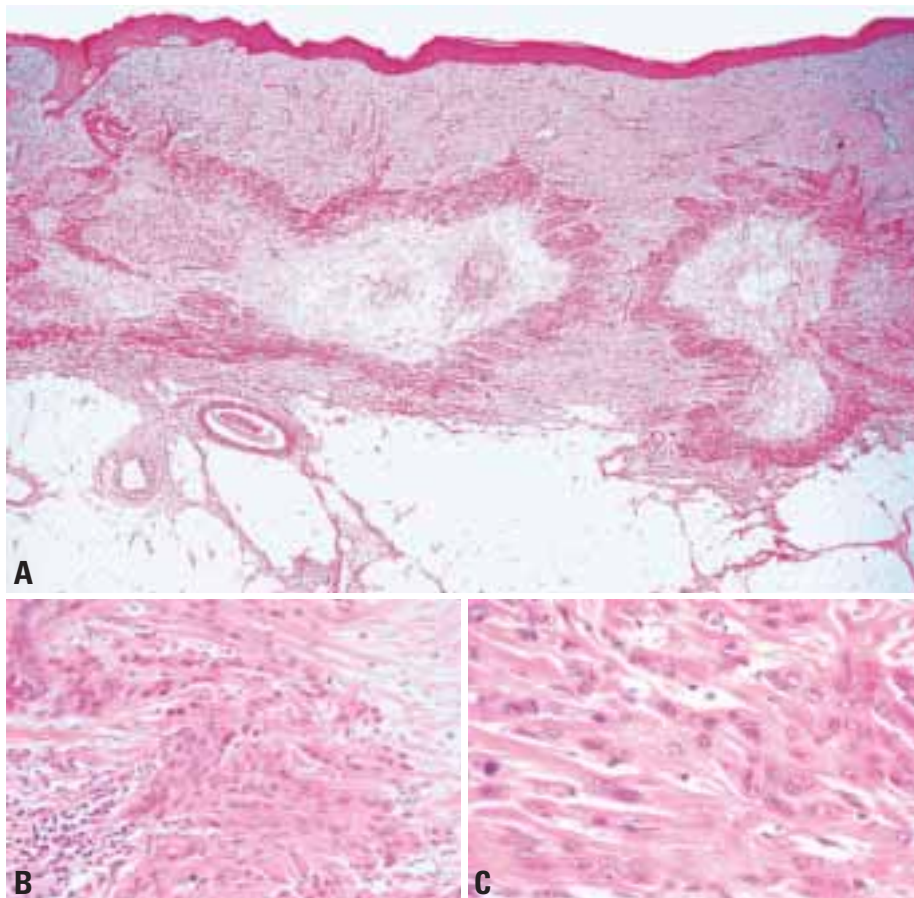


Fig. 9.39 Epithelioid sarcoma. **A** Typical dermal lesion with granuloma-like growth pattern with central necrosis. **B** Tumour cells with a tendency for palisading around central necrotic areas. **C** Cellular details showing abundant ill defined eosinophilic cytoplasm, opened chromatin nuclei, and readily apparent central nucleoli.

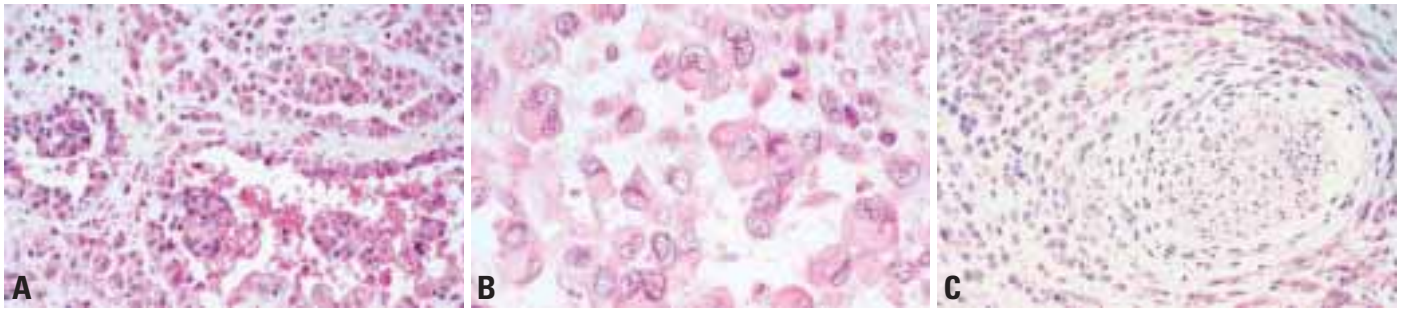


Fig. 9.40 Epithelioid sarcoma. Epithelioid angiosarcoma-like (A) and rhabdoid features (B), as well as perineural invasion (C) are common in conventional epithelioid sarcoma.

abundant collagen-rich extracellular matrix {1446,1473}.

Immunophenotype

Immunohistochemically, ES is characteristically immunoreactive for vimentin and epithelial markers: low- and high-molecular-weight cytokeratins, keratin 8 {1446}, keratin 19 {1446} and/or EMA {432,1324,1397,1446,1888}. Half of the cases are also positive for CD34 {1446,2172}; occasional reactivity for muscle-specific and smooth muscle actins, neuron specific enolase, and S100 protein has also been reported {1446,1888}.

Ultrastructure

Tumour cells show a spectrum of differentiation ranging from epithelial-appearing cells characterized by well formed desmosome-like intercellular junctions, intracytoplasmic aggregates of intermediate filaments (tonofilaments) and/or surface microvilli, to uncommitted fibroblast-like mesenchymal cells {666}.

Genetics

Cytogenetic studies of epithelioid sarcoma are limited to 8 primary or metastatic

tumours and 3 cell lines {398,445,480,646,934,1021,1487,1770,1987,1990,2029}. Six tumours were from typical sites, including the forearm or elbow, and five from atypical sites. Various chromosome deletions and gains, none of which is specific for epithelioid sarcoma, were found in the 11 tumours: 8p-/i(8)(q10) in five tumours, -4, +7/+7p, -9/9p- or 9q-, -13, -16/16p- or 16q-, -18/18p-, and +20 in four tumours, and 1p-, 7q-, +8q, and -22/22q- in three tumours. The only recurrent breakpoints in structural rearrangements were 18q11 and 22q11, seen in two tumours each. It could be noted that while 5/6 cases from typical sites were diploid or hypodiploid, 4/5 tumours from atypical sites showed near-triploidy or near-tetraploidy.

Prognostic factors

ES is an aggressive sarcoma which tends to propagate along fascial planes, and tendon and nerve sheaths. The recurrence rate, which depends mainly on the adequacy of the initial excision, varies between 34% {876} and 77% {336,1810}. Metastases develop in about 40% of the patients, usually following repeat-

ed recurrences, and primarily involve the lungs, but also, in descending order of frequency, regional lymph nodes, scalp, bone, and brain {336,625,1723,1810}. Five- and ten-year overall survival rates range between 50% {336,625} and 80% {231,292}, underlining the characteristic protracted and unpredictable clinical course of the lesion. The overall recurrence rate is about 80% at 10 years {335}.

Adverse prognostic factors in ES include male sex {336}, advanced age at diagnosis, large tumour size (>5 cm) {625}, deep location {231}, nuclear pleomorphism, high mitotic activity, presence of vascular and/or nerve invasion {1723}, multiple recurrences and presence or absence of regional lymph node metastases at diagnosis {292,1723}.

Proximal-type epithelioid sarcoma

Recently, attention has been drawn to a special type of aggressive malignant soft tissue neoplasm thought to represent a «proximal» variant of epithelioid sarcoma {855,897}. In this variant, the tumours develop predominantly (but not exclusive-

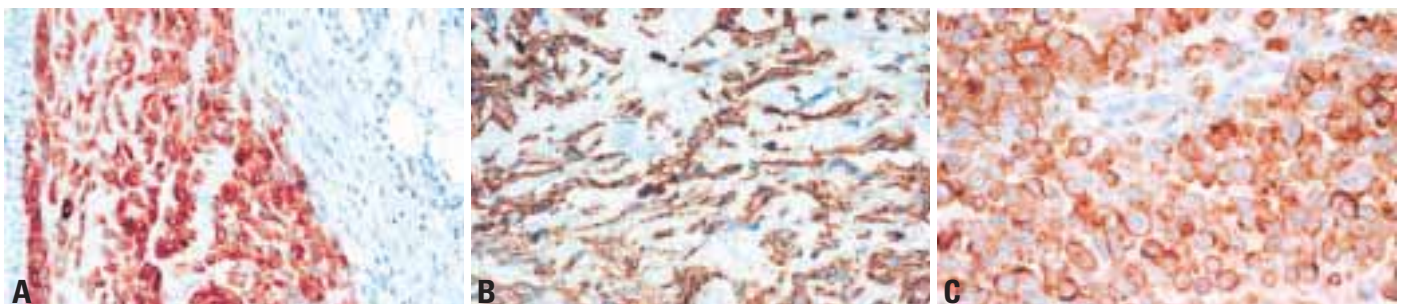


Fig. 9.41 Epithelioid sarcoma. A Tumour cells are positive for cytokeratins. B CD34 immunoreactivity is observed in about 50% of conventional epithelioid sarcomas. C Proximal-type epithelioid sarcoma: tumour cells displaying membranous positivity for EMA

ly) in the pelvis, perineum and genital tract (pubis, vulva, penis). Most of them are deep-seated and they tend to occur in older adults than in the «distal» conventional variant of ES.

Microscopically, «proximal-type» ES, which often shows a multinodular pattern of growth, consists of large epithelioid carcinoma-like cells with marked cytological atypia, vesicular nuclei and prominent nucleoli. Rhabdoid features are frequently observed and may even predominate in some lesions to the point that morphological distinction from a malignant extrarenal rhabdoid tumour (see page 219) may be almost impossible [334,1487,1692]. Rare cases show hybrid histologic features of the classical and proximal subtypes. Tumour necrosis, a common finding, seldom results in a granuloma-like pattern like that observed in the classical «distal» form of ES. Immunohistochemical and ultrastructural features are similar to «distal» ES [855, 897].

Like malignant extrarenal rhabdoid tumours, «proximal-type» ES seems also to be associated with a more aggressive clinical course, multimodal therapy resistance, and earlier tumour-related deaths as compared with the more indolent behaviour of conventional ES [336, 855,897,1397]. It is not clear yet if this unfortunate behaviour is related to the prominent rhabdoid phenotype or merely to classical prognostic factors such as tumour size, depth, proximal / axial location, resectability, or vascular invasion.

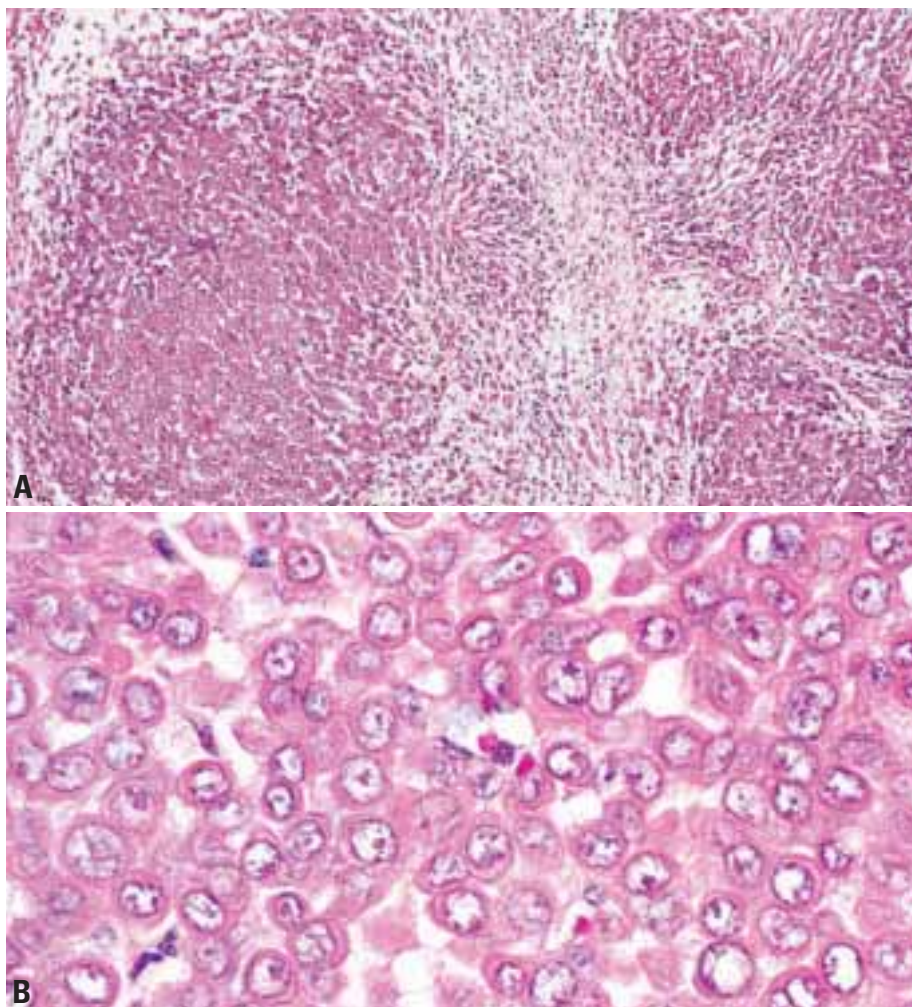


Fig. 9.42 Proximal-type epithelioid sarcoma. **A** Multinodular growth pattern. **B** Tumour cells show abundant and densely eosinophilic cytoplasm, enlarged vesicular nuclei and prominent nucleoli, resulting in a carcinoma-like appearance.

Alveolar soft part sarcoma

N. Ordóñez
M. Ladanyi

Definition

Alveolar soft part sarcoma (ASPS) is a rare tumour affecting mainly adolescents and young adults. It is composed of large, uniform, epithelioid cells having abundant eosinophilic, granular cytoplasm arranged in solid nests and / or alveolar structures, separated by thin, sinusoidal vessels.

ICD-O code 9581/3

Epidemiology

ASPS is a rare tumour with a reported frequency of 0.5% to 0.9% of all soft tissue sarcomas {901, 1227}. It can occur at any age, but is most common between 15 and 35 years. It is rare before 5 and after 50 years of age. There is a female predominance before age 30 and a slight male predominance over age 30 {1617,1719}.

Sites of involvement

In adults, the tumour most commonly occurs in the extremities, especially in the deep soft tissues of the thigh. In 41% of 176 cases from the two largest series, the tumour originated in the thigh or buttock {1258,1719}. In children and infants, the head and neck region, especially the orbit and tongue, is the most common site of origin. Isolated cases have been

reported in a wide variety of unusual locations, including the female genital tract {1563,1742}, mediastinum {691}, lung {1991}, stomach {2321}, and bone {1661}.

Clinical features

ASPS usually presents as a slowly growing, painless mass that is easily overlooked due to its relative lack of symptoms. Early metastasis is a characteristic feature of this tumour and, in a good number of cases, metastasis to the lung or brain is the first manifestation of the disease. Orbital lesions present most commonly with proptosis and lid swelling. Because of the high vascularity of the tumour, on occasion, pulsation or a distinctly audible bruit can occur. Hypervascularity with prominent draining veins can be demonstrated by angiography or contrast-enhanced CT {1285}, and high signal intensity on T1- and T2-weighted images on MRI are highly suggestive of ASPS {2052}.

Macroscopy

Alveolar soft part sarcomas tend to be poorly circumscribed, pale grey or yellowish in colour, and present a soft consistency. Areas of necrosis and haemorrhage are common, especially in the larger tumours.

Histopathology

The most characteristic light microscopic feature is that of an organoid or nesting pattern which is best seen at low magnification. The nests tend to be uniform, but may vary in size and shape. They are separated by delicate partitions of connective tissue containing sinusoidal vascular channels lined by flattened endothelium. Loss of cellular cohesion and necrosis of the centrally located cells in the nests results in the commonly seen pseudo-alveolar pattern and is the source of the descriptive "alveolar" designation. In some instances, especially in infants and children, the tumour may grow as diffuse sheets of cells without an apparent nesting pattern. The individual tumour cells are large round or polygonal and exhibit little variation in size and shape. They contain one or two vesicular nuclei with prominent nucleoli, but on occasion as many as five nuclei can be seen in the same cell. Nuclear atypia is uncommon, but can occur. The cell borders are sharply defined conferring a distinctly epithelioid appearance. The cytoplasm is abundant, eosinophilic, and finely granular but, on occasion, may appear clear or vacuolated. Mitotic figures are uncommon. The cells frequently contain rhomboid or rod-shaped crystalline inclusions that may be faintly

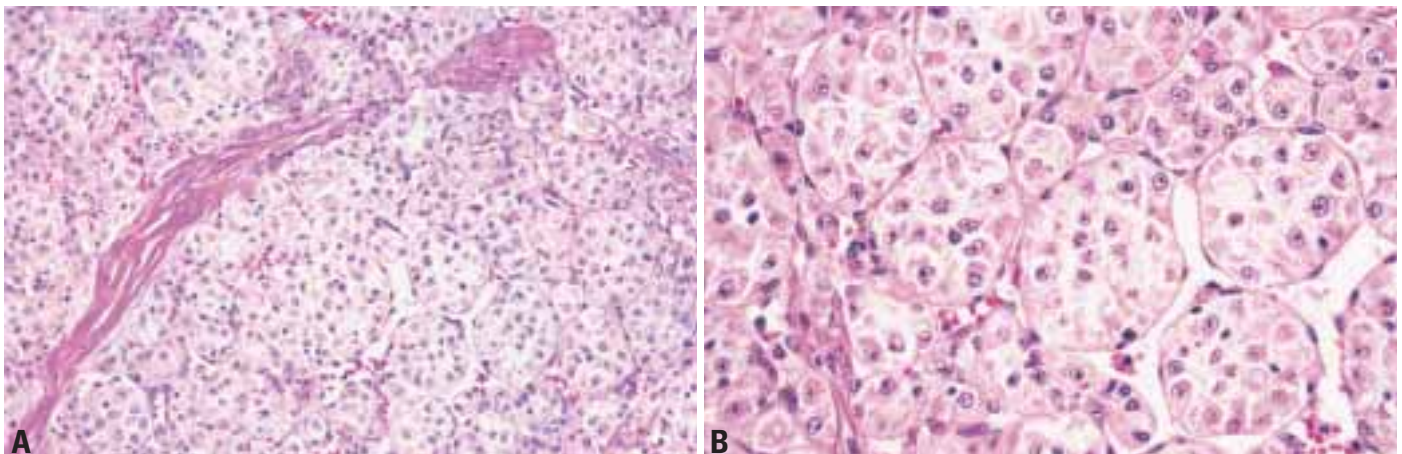


Fig. 9.43 Alveolar soft part sarcoma (ASPS). **A** Low magnification demonstrating the typical organoid pattern. **B** The tumour cell nests are outlined by sinusoidal vascular channels.

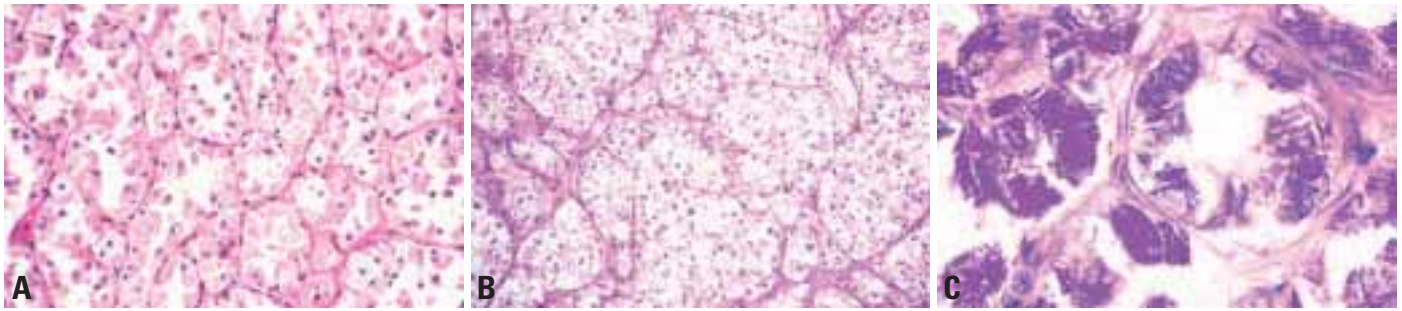


Fig. 9.44 Alveolar soft part sarcoma (ASPS). **A** Area showing the pseudoalveolar pattern. **B** Clearing of the cytoplasm, probably caused by degeneration, can mimic renal cell carcinoma. **C** PAS stain with diastase digestion demonstrates the presence of crystals.

apparent on haematoxylin-and-eosin stained histological preparations but can be better demonstrated with PAS stain after diastase digestion. These inclusions vary greatly in number from case to case. They can be seen in virtually every tumour cell in some cases, while they are rare or even absent in others. In addition to the crystals, variable amounts of glycogen and diastase-resistant granules, which probably represent precursors of the crystals, can also be found. Vascular invasion is an almost invariable feature.

Immunophenotype

ASPS has been extensively studied by immunohistochemical methods with no consistently positive findings {713,1617-1619,2213}. Among the muscle markers that have been investigated, desmin is sometimes positive, particularly in frozen sections, and there is often cytoplasmic (but not nuclear) reactivity for MyoD1. Immunostaining for myogenin has been consistently negative {1618, 2213}. Positivity for S100 protein or neuron-specific enolase has been demonstrated in about one-fourth of the cases, but the expression of these markers has no diagnostic value or significance in the histo-

genesis of this tumour {1617, 1619}. ASPS do not express synaptophysin, chromogranin, neurofilament proteins, cytokeratin, or epithelial membrane antigen.

The majority of cells show moderate to strong nuclear staining with the antibody to the carboxy-terminal portion of TFE3 retained in the fusion protein, in contrast to most normal cells which show only weak to absent nuclear staining with this type of TFE3 antibody {1203}. The PAS-diastase-resistant cytoplasmic granules associated with crystal formation are immunoreactive for MCT1 and CD147 {1202}. MCT1 is a monocarboxylate transporter and CD147 functions, in part, as its chaperon protein.

Ultrastructure

By electron microscopy, the nests of tumour cells are shown to be surrounded by a discontinuous basal lamina. The cell membranes are joined by scattered, poorly developed junctions, and the cytoplasm contains numerous mitochondria, abundant rough endoplasmic reticulum, and prominent Golgi complexes. The most characteristic ultrastructural feature is the presence of membrane-bound or free rhomboid crystals with a

periodicity of 10 nm (see above) {1258, 1619}. Secretory granules containing homogeneous secretory material that on occasion exhibits small foci of crystallization are often seen {1618}.

Genetics

Cytogenetic studies of ASPS have identified a specific alteration, $der(17)t(X;17)(p11;q25)$ {927,1048}. Because the $der(X)$ resulting from the $t(X;17)(p11;q25)$ is almost always absent, the $der(17)t(X;17)$ may be described in some cases as $add(17)(q25)$ unless the quality of the banding allows for positive identification of the additional material as the short arm of X {1907}. This translocation has recently been shown to result in the fusion of the *TFE3* transcription factor gene (from Xp11) with *ASPL* (a.k.a. *ASP-SCR1* or *RCC17*) at 17q25 {1207}. The *ASPL/TFE3* fusion protein localizes to the nucleus and can function as an aberrant transcription factor. Although the presence of the *ASPL/TFE3* fusion appears highly specific and sensitive for ASPS among sarcomas {1207}, the same gene fusion is also found in a small but unique subset of renal adenocarcinomas arising in paediatric and young adult patients {77,928}.

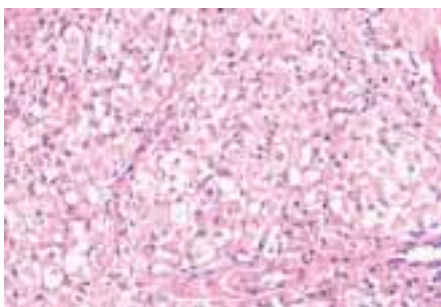


Fig. 9.45 ASPS from the upper limb of an adolescent male. Note the solid growth pattern.

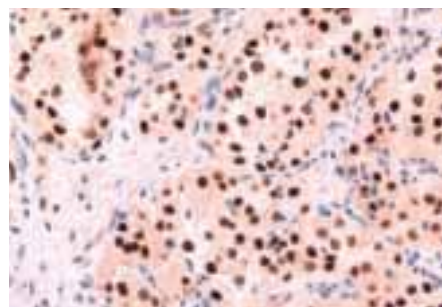


Fig. 9.46 Nuclear staining for TFE3 in a case of alveolar soft part sarcoma (ASPS).



Fig. 9.47 Partial karyotype of ASPS showing the characteristic $der(17)t(X;17)(p11.2;q25)$.

Prognostic factors

ASPS is characterized by relatively slow growth and seldom recurs locally after complete resection; however, it is highly metastatic. Metastasis can occur early in the course of the disease, sometimes prior to the detection of the primary lesion, or much later, even decades, after resection of the primary, despite the absence of local recurrence [95, 1258, 1261, 2191]. In a large study from the Memorial Sloan-Kettering Cancer Centre, the survival rate for patients with no evidence of metastasis at the time of diagnosis was 60% at 5 years, 38% at 10 years, and 15% at 20 years [1258].

Factors that can influence prognosis are patient age at presentation, tumour size, and the presence of metastasis at diagnosis. Histological features have no prognostic significance. It has been reported that there is an increase in the risk of metastasis with increasing age

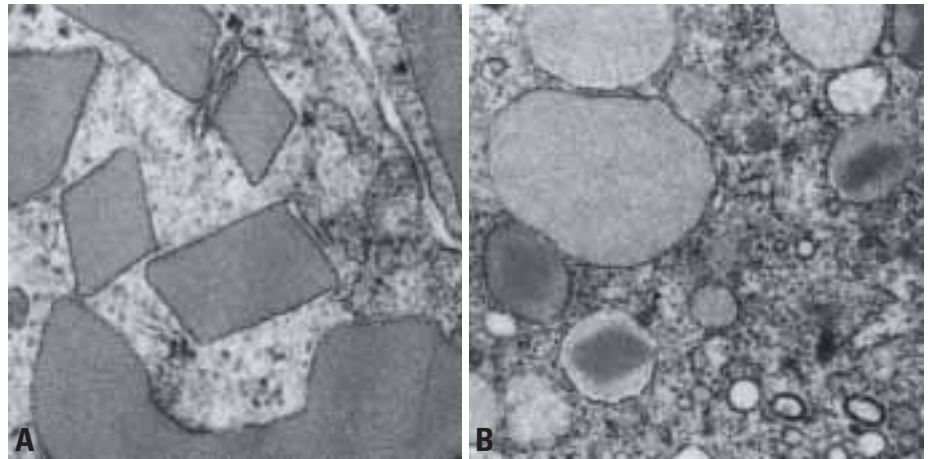


Fig. 9.48 Alveolar soft part sarcoma (ASPS). **A** Membrane-bound, fully developed crystals may adhere to one another, forming a variety of shapes. **B** Some of the large, membrane-bound secretory granules contain foci of crystallization.

{1258} and that patients who present with larger tumours are most likely to have metastasis at the time of diagnosis [618]. The most common sites of metas-

tasis in decreasing order of frequency are lung, bone, and brain [1258,1719]. Metastasis to the lymph nodes is uncommon.

Clear cell sarcoma of soft tissue

R. Sciot
F. Speleman

Definition

A soft tissue sarcoma of young adults with melanocytic differentiation, typically involving tendons and aponeuroses. This tumour is unrelated to paediatric lesions currently known as clear cell sarcoma of the kidney.

ICD-O code 9044/3

Synonym

Malignant melanoma of soft parts.

Epidemiology

These rare tumours usually affect young adults, with a peak incidence in the third and fourth decade. Presentations under the age of 10 or above 50 years are rare. There is a slight female predominance {354,484,567,589,1291,1499}.

Sites of involvement

The extremities are the principal site of involvement (90-95%) with the foot/ankle region accounting for about 40% of cases. Clear cell sarcoma is usually deep seated and often attached to aponeuroses and tendons. The tumour may extend into the subcutis or lower dermis, but the epidermis is typically intact. The head and neck and the trunk region are rarely involved {354,484,567,589,1291,1499}. The visceral organs, retroperitoneum, bone, penis and spinal nerve roots are exceptional locations {535,573,731,1347,1662,1817,1866,2065,2324}.

Clinical features

The tumour usually presents as a slowly growing mass, being present for several weeks to several years. Pain and/or tenderness is present in up to 50% of cases. On MRI imaging, clear cell sarcoma usually has a benign looking appearance with a slightly increased intensity on T1-weighted images compared to muscle in about half the cases {465}.

Macroscopy

Most tumours are relatively small (2-6 cm), although lesions as large as 15 cm

have been described. The cut surface usually shows a lobulated grey-white mass. Pigmented areas are found in rare cases. Necrosis or cystic degeneration is occasionally seen.

Histopathology

Clear cell sarcoma shows a typical uniform, nested to fascicular growth pattern. Tumour cells are polygonal or spindle-shaped with abundant eosinophilic or clear cytoplasm. The nuclei are typically vesicular with a prominent nucleolus. Thin fibrous septa delineate the tumour cell nests. Scattered wreath-like multinucleated giant cells are present in about 50% of cases. The mitotic activity is usually relatively low as also is the degree of pleomorphism. Melanin is rarely seen on H&E stains, but can be detected by melanin stains in +/-50% of cases {354,484,567,589,1291,1499}. Less common morphological variations on the typical appearance, are: spindle cell arrangement, marked pleomorphism and mitotic activity (especially in recurrent and

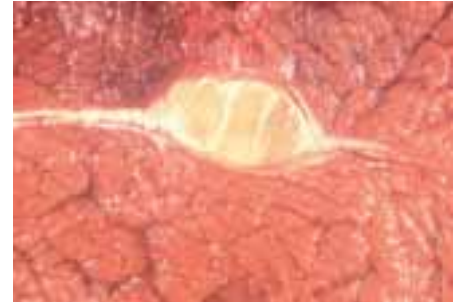


Fig. 9.49 Clear cell sarcoma. This well circumscribed tumour arose in the plantaris tendon of an 18-year-old woman. Despite the small size of the tumour, she died from disseminated metastases four years later.

metastatic lesions), solid round cell aspect, microcystic aspect, and the presence of myxoid stroma {354,416,484,567,589,1291,1499}.

Immunophenotype

Positivity for S100 protein, HMB45 and other melanoma antigens is seen in almost all cases {829,1115,1291,1499,

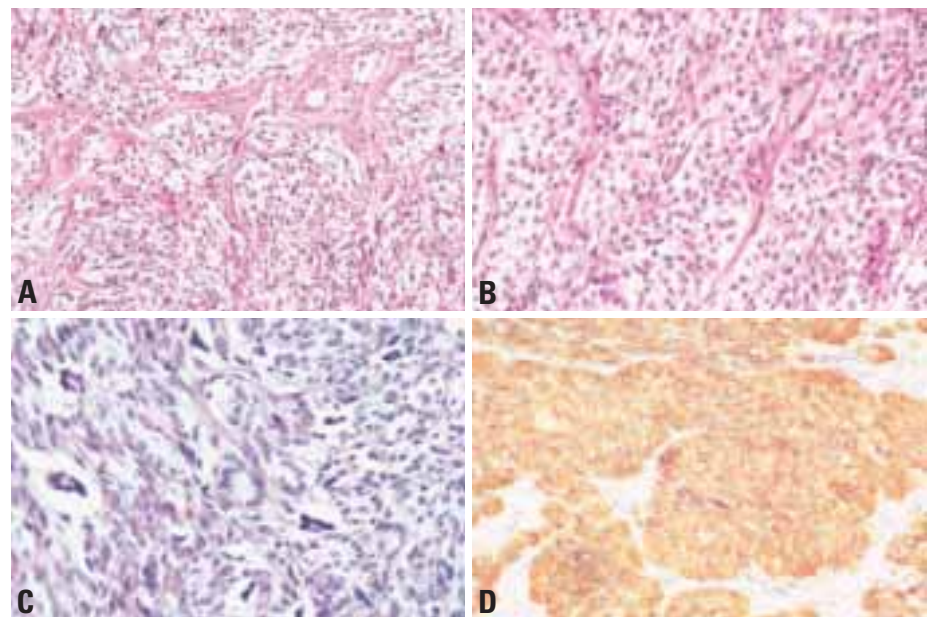


Fig. 9.50 Clear cell sarcoma. **A** Nests of clear polygonal cells delineated by fibrous septa. **B** Typical clear cell sarcoma with more eosinophilic cytoplasm. Note the prominent vesicular nuclei and nucleoli. **C** Area showing wreath-like giant cells. **D** Strong S100 staining is a consistent feature.

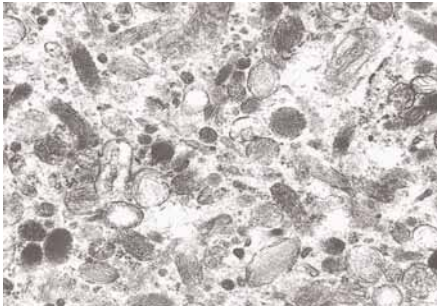


Fig. 9.51 Ultrastructural appearance of clear cell sarcoma from a 23 year-old male, showing a mixture of stage II and III melanosomes.

2065}. Positivity for HMB45 is often stronger and more diffuse than for S100 protein. Expression of neuron-specific enolase, synaptophysin, CD57 (Leu-7), and even cytokeratin and actin have been noted {416,1291,1499,1501,2065}.

Ultrastructure

Melanosomes in varying stages of development are present in the majority of cases. Variably abundant cytoplasmic glycogen, swollen mitochondria and a basal lamina complete the picture {1115, 1453, 1517}.

Genetics

The cytogenetic hallmark of clear cell sarcoma is the presence of a reciprocal translocation, $t(12;22)(q13;q12)$. This translocation has been detected in the majority of clear cell sarcoma cases reported in the literature but not in other malignancies {1477}. The $t(12;22)(q13;q12)$ results in fusion of the

EWS (22q12) and *ATF1* (12q13) genes {74, 2350}.

The $t(12;22)$ has been reported as the sole chromosomal aberration in clear cell sarcoma, however, most cases also display additional chromosomal aberrations, often complex in nature. These additional cytogenetic changes include +8, structural and numerical aberrations involving chromosome 22 (other than the $t(12;22)$) and +7 {1262, 2007, 2128}. No variant or cryptic translocations, resulting in an *EWS/ATF1* fusion transcript have been reported.

The *EWS/ATF1* fusion protein invariably contains the N-terminal domain of *EWS* and the *ATF1* bZIP domain. An *EWS/ATF1* fusion transcript is detectable with RT-PCR in more than 90% of the cases {74}. The type 1 fusion transcript (*EWS* exon 8-*ATF1* codon 65) is by far the most common, but other variants account for approximately 10% of the cases. The reciprocal *ATF1/EWS* transcript probably does not contribute to malignant conversion, since it is out of frame. *ATF1* is a member of the CREB/ATF basic leucine-zipper type of transcription factor family and binds to cAMP inducible promoters. It was shown that the *EWS/ATF1* fusion converts *ATF1* to a constitutive transcriptional activator that represses TP53/CBP-mediated transactivation {728,729}.

By RT-PCR analysis it was shown that 4/4 cases expressed the melanocyte-specific splice form of the microphthalmia transcription factor (*MITF*) transcript {74}.

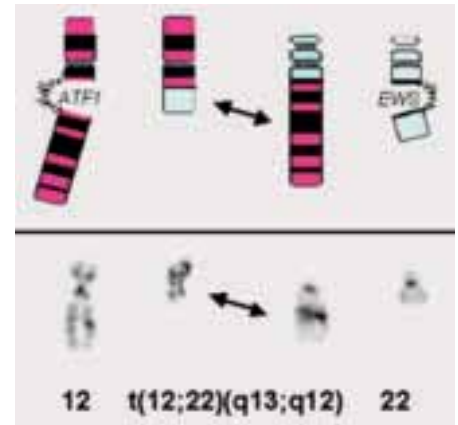


Fig. 9.52 Schematic and partial G-banded karyotype illustrating the 12;22 translocation characteristic of clear cell sarcoma.

Prognostic factors

The prognosis is poor with a mortality rate ranging from 37% to 59% in the largest series {354,484,567,589,1291, 1499}. Many patients develop recurrences and metastases, albeit sometimes more than 10 years after diagnosis. Five-year survival figures thus overestimate the long term survival. In the Mayo Clinic series, the survival at 5, 10 and 20 years was 67%, 33% and 10%, respectively {1291}. Nodal metastasis develops in up to 50% of patients. There is as yet no answer to the question of prophylactic regional lymph node dissection. The lung and bone are other frequent sites of metastasis. Tumour size (greater than 5 cm), necrosis and local recurrence are unfavourable prognostic factors {1291, 1499,1862}.

Extraskelletal myxoid chondrosarcoma

D.R. Lucas
S. Heim

Definition

Extraskelletal myxoid chondrosarcoma (EMC) is a malignant soft tissue tumour characterized by a multinodular architecture, abundant myxoid matrix, and malignant chondroblast-like cells arranged in cords, clusters, or delicate networks. Despite the name, there is no convincing evidence of cartilaginous differentiation.

ICD-O code 9231/3

Synonym

Chordoid sarcoma.

Epidemiology

EMC is a rare tumour, accounting for less than 3% of soft tissue sarcomas [2143]. It is primarily a tumour of adulthood with the median age in the sixth decade and a male:female ratio of 2:1. Only rare cases in childhood or adolescence have been reported [864].

Sites of involvement

Most EMCs arise in the deep soft tissues of the proximal extremities and limb girdles [597,1385]. Thigh is the most common location. Less common sites include trunk, paraspinal region, foot, and head and neck region. Rare tumours have also been reported in the finger [1603], intracranial location [1864], retroperitoneum [730], pleura [801], and bone [1105].

Clinical features

Patients typically present with an enlarging soft tissue mass. Pain and tenderness characterize some cases, and tumours around joints may restrict range of motion. Large or superficial tumours may ulcerate the skin. Although imaging characteristics are nonspecific, most tumours appear lobulated, and highly myxoid tumours have a homogeneous high signal on T2 weighted MRI image. Tumours with necrosis or hemorrhage have a more heterogeneous signal.

Macroscopy

Most EMCs form large, well demarcated tumours contained by a pseudocapsule.

The median size is 7 cm [1385]. However, tumour size is quite variable, including very large masses (20-25 cm) in some cases. On cut section, the tumour has a well defined multinodular architecture comprised by gelatinous nodules separated by fibrous septa. Intratumoural cysts and haemorrhage, both recent and remote, and geographic areas of necrosis may be present. Highly cellular tumours have a fleshy consistency.

Histopathology

Conventional 'well differentiated' EMC has a multinodular architecture defined by fibrous septa that divide the tumour into circumscribed areas filled with pale blue myxoid or chondromyxoid stroma that is rich in sulfated proteoglycans. Lobules often show higher cellularity at the periphery. Well formed hyaline cartilage is rarely, if ever seen. The stroma is strikingly hypovascular.

The neoplastic cells usually have a modest amount of deeply eosinophilic, finely granular to vacuolated cytoplasm and uniform round to oval nuclei. The chromatin is usually evenly distributed often with a small, inconspicuous nucleolus. The cells characteristically interconnect with one another to form cords or clus-



Fig. 9.53 Extraskelletal myxoid chondrosarcoma typically forms a demarcated tumour encased by a pseudocapsule, and divided into multiple gelatinous nodules by fibrous septa. Intratumoural cysts and hemorrhage are common.

ters. In some tumours they form complex, filigree or cribriform arrays, while others show spindle cell patterns. Epithelioid cells with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli, or rhabdoid cells with hyalinized cytoplasmic globules, are found in some EMCs. Mitotic activity is usually low (<2 mitotic figures per 10 high power field) in most cases. Areas of recent and remote intratumoural haemorrhage are common.

EMC may have more cellular areas, characterized by closely spaced cells with

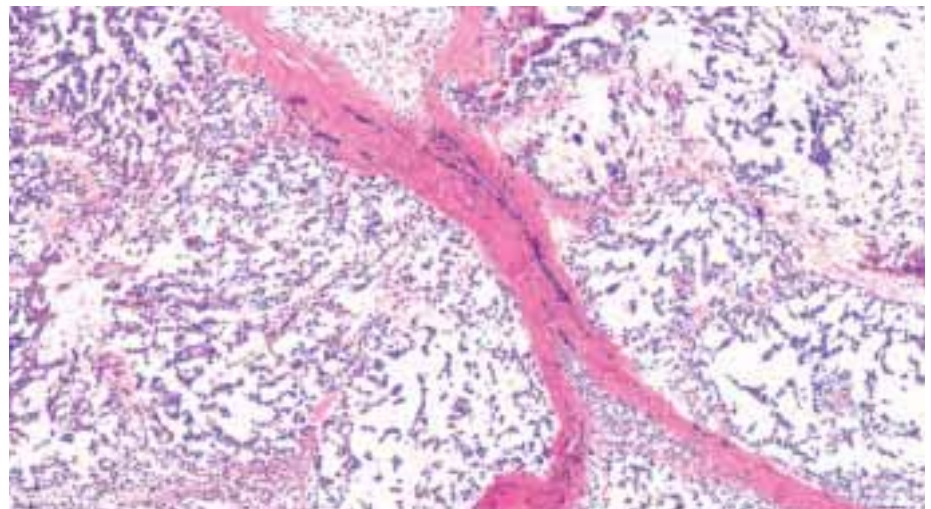


Fig. 9.54 On low power, extraskelletal myxoid chondrosarcoma has a multinodular architecture consisting of myxoid areas demarcated by fibrous septa.

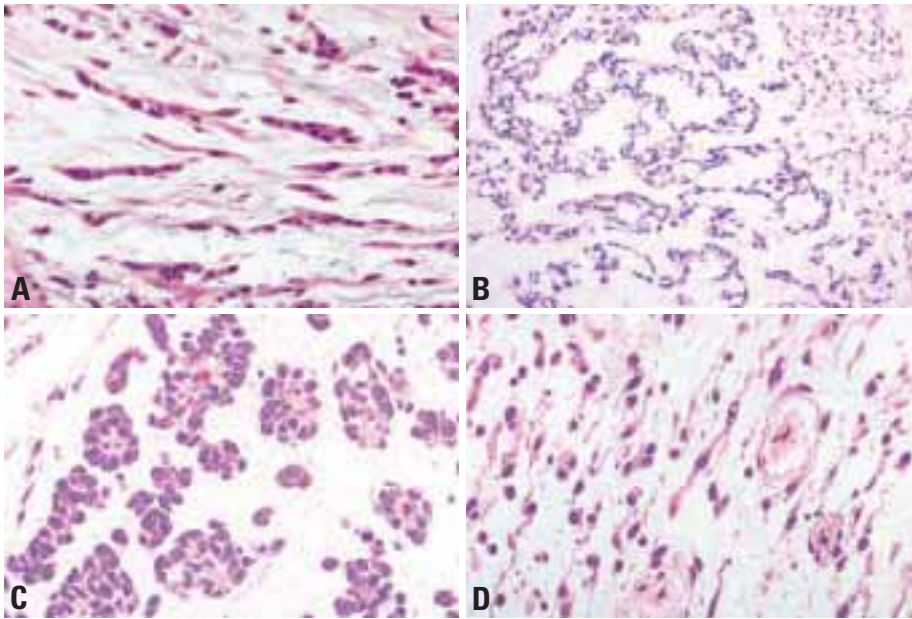


Fig. 9.55 Extraskeletal myxoid chondrosarcoma (EMC). Tumour cells typically have low grade cytologic features and interconnect with one another to form (A) cords, (B) delicate networks, (C) clusters, or (D) spindle cell patterns.

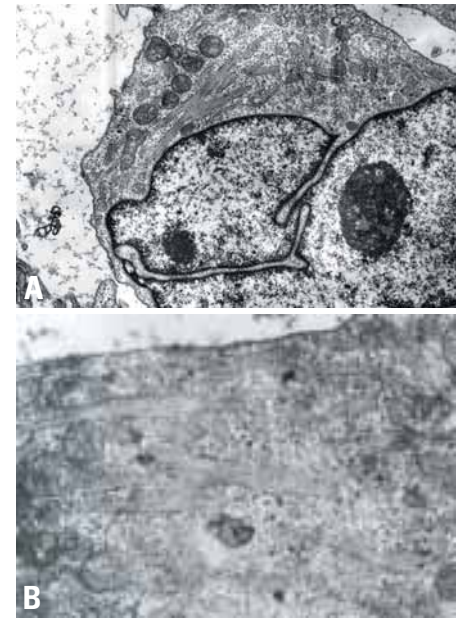


Fig. 9.56 A,B EM features of EMC include granular extracellular matrix, cytoplasm rich in mitochondria and RER, and intracisternal microtubules.

minimal myxoid stroma. Diffusely cellular tumours are referred to as "cellular variants". The cells in these tumours frequently have epithelioid morphology and greater mitotic activity. Some EMCs display sheets of anaplastic epithelioid cells devoid of matrix, fibrosarcomatous areas, brisk mitotic activity with abnormal division figures, and large geographic areas of necrosis. In such high grade tumours, one may need to search for areas of conventional EMC morphology in order to make the diagnosis. Finally, small cells with scant cytoplasm may comprise some EMCs {864, 1385}.

Immunophenotype

Vimentin is the only marker consistently expressed in EMC {494,1385}. S100 protein, cytokeratin, and epithelial mem-

brane antigen are expressed in a minority of tumours and usually only focally. Synaptophysin or neuron-specific enolase expression has been demonstrated in some tumours {889,1603,1611}.

Ultrastructure

Interconnecting, rounded mesenchymal cells surrounded by abundant granular amorphous extracellular stroma characterize its fine structure. The cytoplasm is rich in organelles, especially mitochondria, rough endoplasmic reticulum (RER), and intermediate filaments, which are sometimes arranged in perinuclear whorls. Dilations within the RER filled with granular amorphous material identical to the extracellular stroma, and ruffled cytoplasmic borders are common findings. Intracisternal microtubules are very char-

acteristic of EMC. However, they are present in less than half the cases {65, 1385, 1672}. Dense core neurosecretory granules have also been report in some cases {889}.

Genetics

Myxoid chondrosarcoma has been examined both at the cytogenetic and molecular genetic levels. Of the more than 20 such tumours that have been reported to carry clonal chromosomal aberrations {205,253,266,459,949,950, 1332,1633,2028,2144}, the reciprocal translocation t(9;22)(q22;q12) was seen in around half of all cases. Sometimes three-way variant translocations were observed, and more often than not there are additional, secondary chromosomal aberrations. The t(9;22) (q22;q12) has

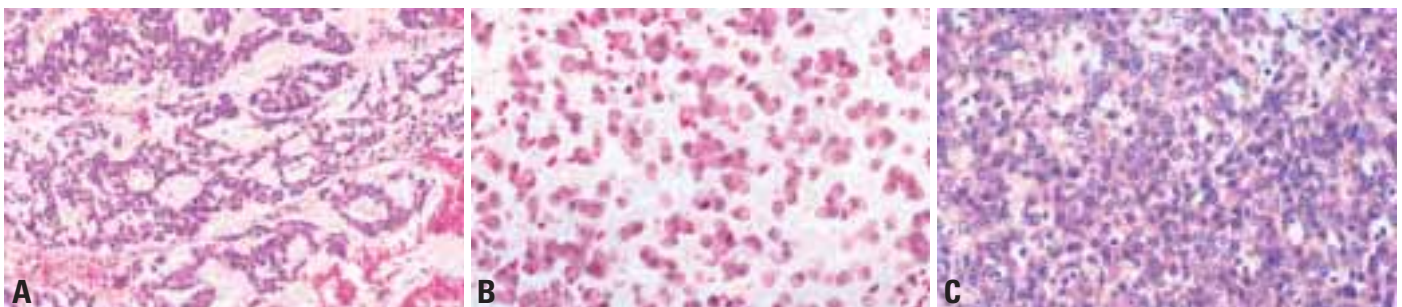


Fig. 9.57 Extraskeletal myxoid chondrosarcoma (EMC). A In some tumours the cells form complex cribriform arrays. B Rhabdoid cells with eccentric hyaline globules, are occasionally seen in EMC. C 19 Densely cellular areas with minimal matrix characterize the cellular higher grade variant of EMC.

not been associated with other diagnostic entities. A second cytogenetic subgroup of extraskeletal myxoid chondrosarcoma characterized by the presence of a $t(9;17)(q22;q11)$ was also identified [205]; this translocation is equally specific but less common than the $t(9;22)$.

The molecular genetic consequences of both the $t(9;22)(q22;q12)$ and the $t(9;17)(q22;q11)$ have been unravelled [359,1201,1643,1963]. In the former translocation, the genes *NR4A3* (a.k.a. *CHN*, *TEC*, from 9q22) and *EWS* (from 22q12) are fused. It seems that two main *EWS/NR4A3* transcripts exist, joining *EWS* exons 12 and 7, respectively, to *NR4A3*. In the $t(9;17)(q22;q11)$, *NR4A3* is recombined instead with the *RBP56* gene from 17q11 to generate a chimeric *RBP56/NR4A3*. *RBP56* encodes a putative RNA-binding protein similar to the *EWS* and *FUS* proteins. It appears that the N-terminal parts of *EWS* and *RBP56* have similar oncogenic potential making them pathogenetically equivalent in oncoproteins arising from fusions with certain transcription factors. A third chromosomal variant, $t(9;15)(q22;q21)$, which has been described in a single case, leads to the fusion of the *TCF12* and *NR4A3* genes [1964].

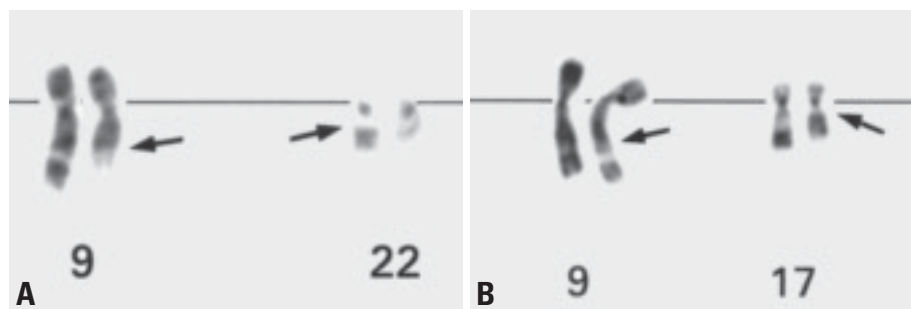


Fig. 9.58 **A** The translocation $t(9;22)(q22;q12)$ (arrows indicate breakpoints) is pathognomonic for extraskeletal myxoid chondrosarcoma and is found in half of all such tumours. It recombines the two genes *NR4A3* (from 9q22) and *EWS* (from 22q12). **B** The translocation $t(9;17)(q22;q11)$ (arrows indicate breakpoints) is also typical for extraskeletal myxoid chondrosarcoma but is found only in a minority of lesions. It recombines the genes *NR4A3* (from 9q22) and *RBP56* (from 17q11).

Prognostic factors

EMC is a tumour with long survival but is known, with prolonged follow-up, to have high potential for local recurrence and metastasis, and a high disease-associated death rate [1385,1847]. Local recurrences and metastases each occur in approximately half of cases. Metastases are usually pulmonary. However, extrapulmonary and disseminated metastases also occur [1847]. Interestingly, prolonged survivals even in the face of metastatic disease are not uncommon in EMC. In a recent large study of 99 patients, Meis-Kindblom et al. [1385]

report 5, 10, and 15 year survivals of 90, 70, and 60%, respectively.

Large tumour size, especially greater than 10 cm, appears to be a significant negative prognostic factor in EMC [1385, 1611]. Although a number of studies deny the significance of histologic variables such as grade, cellularity, and mitotic rate on clinical behaviour [1028, 1385,1847], others suggest that examples showing increased cellularity and atypia are more aggressive [65, 1289, 1611]. A few studies have also suggested that the presence of rhabdoid cells may be an adverse histologic variable [1611,1622].

Malignant mesenchymoma

H.L. Evans

The term "malignant mesenchymoma" has been applied to sarcomas that exhibit two or more lines of specialized differentiation. However, it has become apparent that this group does not form a clinicopathological entity, and that potential candidates for the designation can be more appropriately classified in other ways. Among those with a fatty component are myxoid liposarcomas with carti-

laginous metaplasia, atypical lipomatous tumours (well differentiated liposarcomas) with osseous, cartilaginous, smooth muscle, or skeletal muscle elements, dedifferentiated liposarcomas with the same elements in the dedifferentiated component, and pleomorphic liposarcomas with osteogenic areas. Nonfatty neoplasms meeting the definition include the rare leiomyosarcomas

that have osteosarcomalike or rhabdomyosarcomatous zones and the occasional embryonal rhabdomyosarcomas that demonstrate focal cartilage. Obviously all of these are different neoplasms, and "lumping" them together under one heading is misleading.

ICD-O code 8990/3

Desmoplastic small round cell tumour

C.R. Antonescu
W. Gerald

Definition

Desmoplastic small round cell tumour (DSRCT) is composed of small round tumour cells of uncertain histogenesis, associated with prominent stromal desmoplasia and polyphenotypic differentiation. The presence of the t(11;22) (p13;q12) translocation is a consistent cytogenetic feature.

ICD-O code 8806/3

Synonyms

Intraabdominal desmoplastic small round cell tumour, intrabdominal desmoplastic small cell tumour with divergent differentiation, polyphenotypic small round cell tumour.

Epidemiology

DSRCT primarily affects children and young adults, who usually present with

widespread abdominal serosal involvement {777}. There is a striking male predominance, with a peak incidence in the third decade of life (with a wide range from 1st to 5th decade).

Sites of involvement

The vast majority of patients develop tumour in the abdominal cavity, frequently located in the retroperitoneum, pelvis, omentum, and mesentery. Multiple serosal implants are common. Clinical presentation outside the abdominal cavity is

very rare, and is mainly restricted to the thoracic cavity and paratesticular locations {412}. Isolated cases occur in limbs, head and neck and brain.

Clinical features

Presenting symptoms are usually related to the primary site, such as pain, abdominal distension, palpable mass, acute abdomen, ascites, and organ obstruction. Presentation at an exceptional site (see above) should prompt a careful search for an intra-abdominal primary.



Fig. 9.59 Desmoplastic small round cell tumour presenting as one dominant tumour mass and multiple smaller tumour nodules. The cross section shows a solid white-tan cut surface, with foci of necrosis.

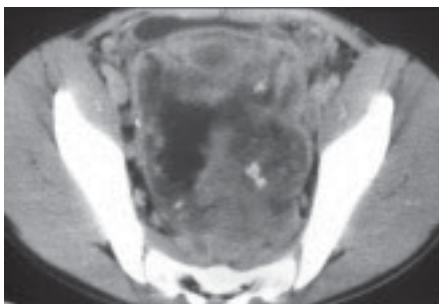


Fig. 9.60 CT image of a large pelvic desmoplastic small round cell tumour.

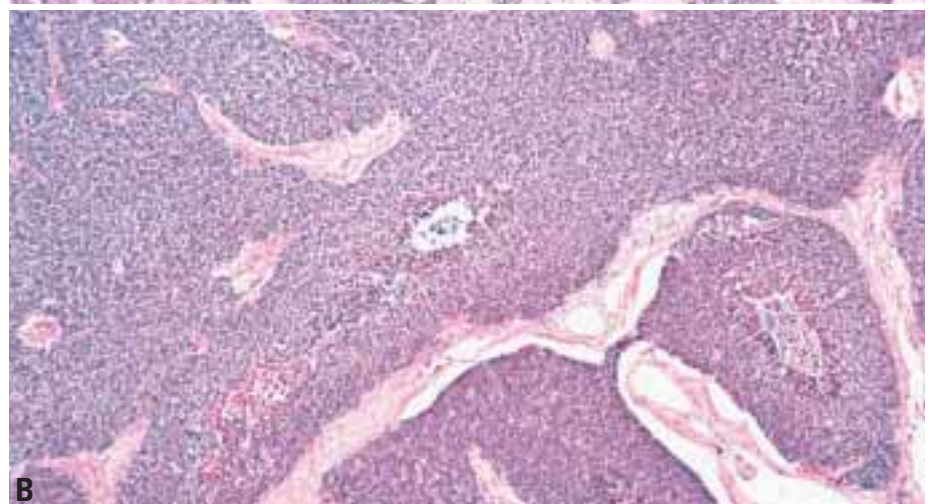
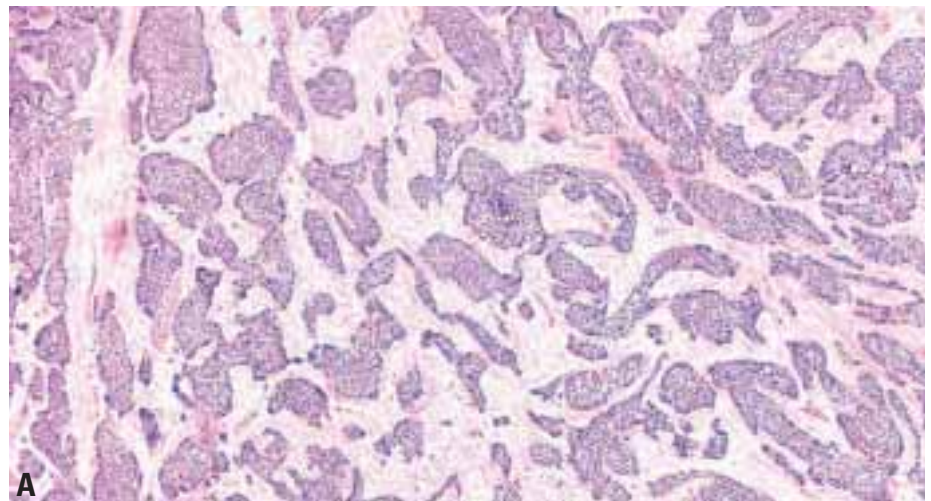


Fig. 9.61 Histological spectrum of desmoplastic small round cell tumour. **A** Characteristic morphology with variably sized nests in a desmoplastic stroma. **B** Solid growth pattern with large confluent nests.

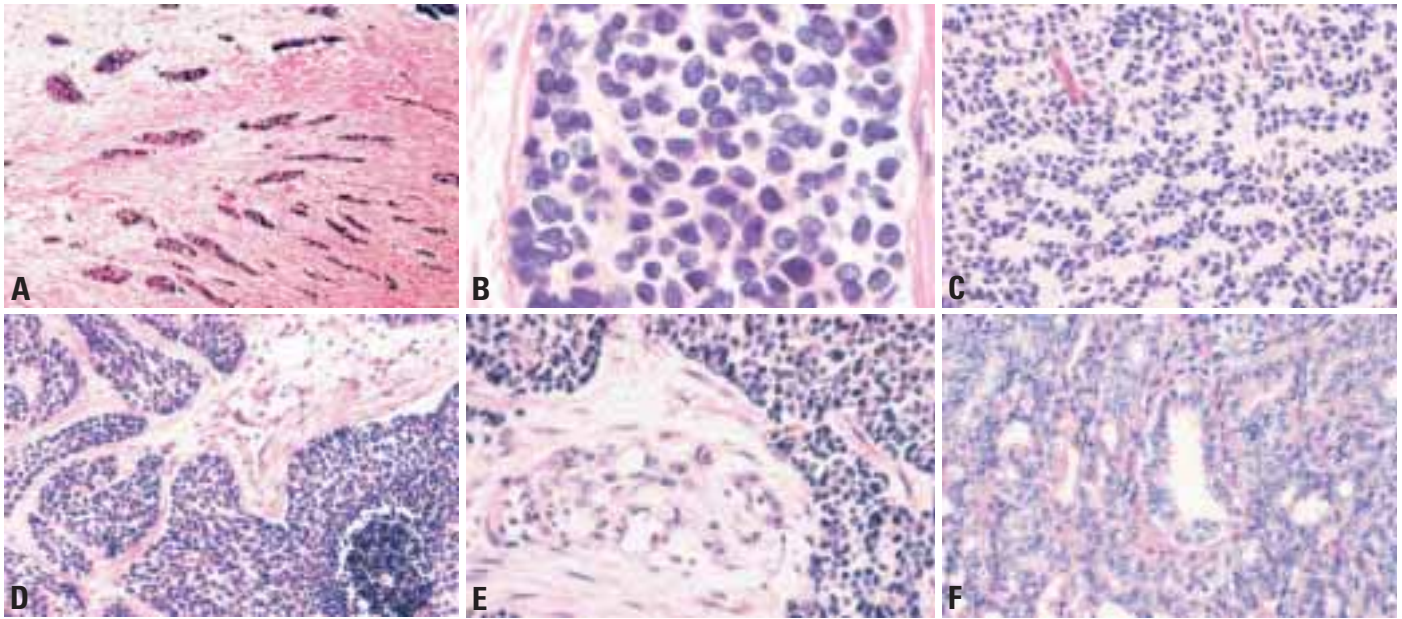


Fig. 9.62 Histological spectrum of desmoplastic small round cell tumour (DSRCT). **A** Infiltrative growth pattern and "indian-file" appearance. **B** Small round cells with minimal nuclear pleomorphism. **C** Rosette formation. **D** Focal necrosis. **E** "Glomeruloid" vascular proliferation. **F** Epithelial features with gland formation.

Macroscopy

The typical gross appearance consists of multiple tumour nodules studding the peritoneal surface. Often there is a dominant tumour mass accompanied by smaller nodules. The cut surface is firm, grey-white, with foci of haemorrhage and necrosis.

Histopathology

Histologically, DSRCT is characterized by variably sized and shaped, sharply outlined nests of small neoplastic cells surrounded by a prominent desmoplastic stroma. The size of the nests varies considerably, from minute clusters to large irregular confluent sheets. Central necrosis is common and cystic degeneration can also be seen. Some tumours focally exhibit epithelial differentiation, with glands or rosette growth pattern. The

tumour cells are typically uniform with small hyperchromatic nuclei, scant cytoplasm and indistinct cytoplasmic borders. In about half of cases a small component of tumour cells show intracytoplasmic eosinophilic rhabdoid inclusions. Some tumours have larger cells and greater pleomorphism. The chromatin is typically dispersed, with inconspicuous nucleoli. Mitoses are frequent and individual tumour cell necrosis is common. The desmoplastic stroma is composed of fibroblasts or myofibroblasts embedded in a loose extracellular material or collagen. Prominent stromal vascularity is also present, suggestive of a hyperplastic response to the tumour. The hyperplastic vessels vary from complex capillary tufts to larger vessels with eccentric thickened walls and prominent endothelial and pericytic cells.

Immunophenotype

The immunoprofile of DSRCT is consistent and distinctive, showing a complex pattern of simultaneous multi-phenotypic differentiation, expressing proteins associated with epithelial, muscular, and neural differentiation {778, 779}. The majority of cases are immunoreactive for cytokeratins, epithelial membrane antigen, vimentin, desmin, and NSE. A distinctive dot-like intracytoplasmic localization is seen with desmin and occasionally with other intermediate filaments. Myogenin and myoD1 are consistently negative. Nuclear expression of WT1 (using antibodies to the carboxy terminus) is usually seen {124, 947}. The stromal component is positive for vimentin and common or smooth muscle actin, suggesting myofibroblastic origin.

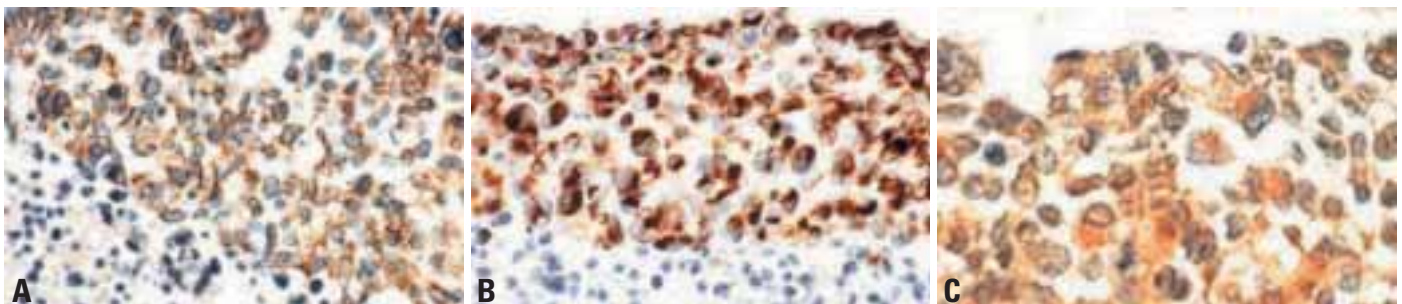


Fig. 9.63 Immunoprofile of DSRCT: strong immunoreactivity for cytokeratin (A), desmin (B), and NSE (C).

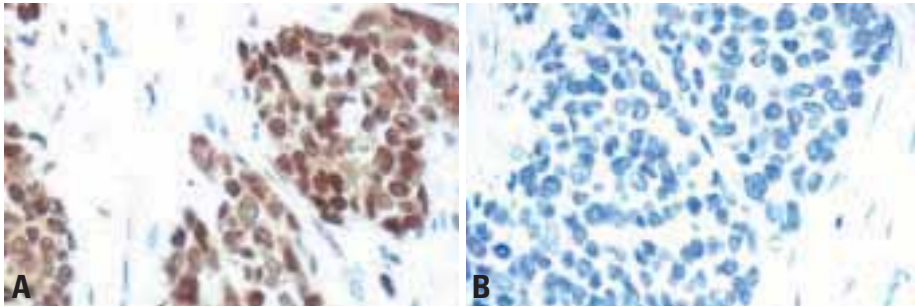


Fig. 9.64 Immunodetection of EWS/WT1 chimeric protein in desmoplastic small round cell tumour (DSRCT). **A** Strong nuclear reactivity with the WT1 (C19) antibody directed to the carboxy terminus of WT1. **B** No reactivity with the WT1 antibody directed to the amino terminus of WT1.

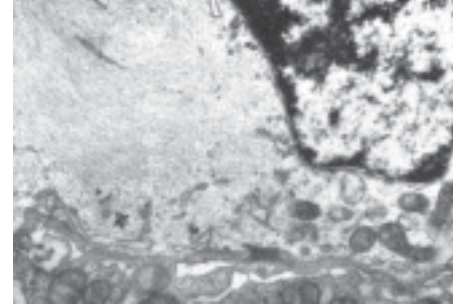


Fig. 9.65 EM of DSRCT: neoplastic cells with typical whorls of intermediate filaments and well formed desmosome junctional structures.

Ultrastructure

Most cells have a primitive / undifferentiated appearance with small amounts of cytoplasm and scant organelles. A notable feature is the presence of paranuclear aggregates and whorls of intermediate filaments. Rare dense core granules can be also seen in some cases. Few cells are connected by cell junction complexes, including well formed desmosomes.

Genetics

DSRCT is characterized by a specific chromosomal abnormality, $t(11;22)(p13;q12)$ {190,1801,1871}, unique to this tumour, involving two chromosomal regions previously implicated in other

malignant tumours. The translocation results in the fusion of the Ewing sarcoma gene, *EWS*, on 22q12 and the Wilms tumour gene, *WT1*, on 11p13 {461, 780, 1206}. Interestingly, the most common primary site of DSRCT, the serosal lining of body cavities, has high transient fetal expression of *WT1* gene. *WT1* is expressed in tissues derived from the intermediate mesoderm, primarily those undergoing transition from mesenchyme to epithelium, in a specific period of development {1729,1751}. This stage of differentiation is reminiscent of DSRCT with early features of epithelial differentiation.

The most commonly identified *EWS/WT1* chimeric transcript is composed of an in-

frame fusion of the first seven exons of *EWS*, encoding the potential transcription modulating domain, and exons 8 through 10 of *WT1*, encoding the last three zinc-fingers of the DNA-binding domain. Rare variants including additional exons of *EWS* occur {70}. Intranuclear chimeric protein can be detected and shown to contain the carboxy terminus of *WT1* {776}. Detection of the *EWS/WT1* gene fusion and chimeric transcript serves as a sensitive and specific marker for DSRCT {776}.

Prognostic factors

The overall progression-free survival remains very poor, despite multimodal therapy {776,1189}.

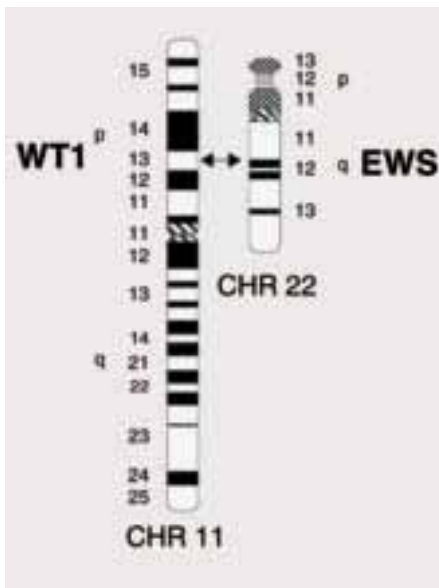


Fig. 9.66 Diagrammatic representation of chromosomal breakpoints in DSRCT with $t(11;22)(p13;q12)$ translocation.

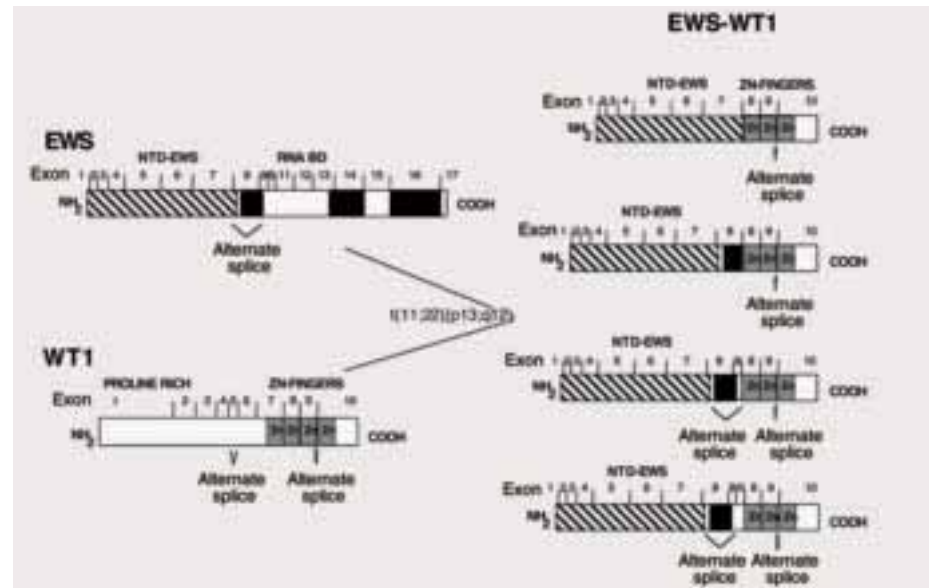


Fig. 9.67 Diagrammatic representation of chromosomal breakpoints in DSRCT with *EWS/WT1* fusion transcripts. All chromosome 11 breakpoints involve intron 7 of *WT1*, suggesting that the preservation of the last three zinc-finger motifs of *WT1* is crucial to sarcomagenesis. The majority of chromosome 22 breakpoints involve intron 7 of *EWS* and, infrequently, introns 8 and 9.

Extrarenal rhabdoid tumour

D. Schofield

Definition

Soft tissue rhabdoid tumour is a malignant tumour of infants and children, characterized by neoplastic cells with large nuclei, prominent nucleoli, and abundant, eccentric cytoplasm with variably prominent eosinophilic, cytoplasmic "inclusions". These inclusions are ultrastructurally composed of whorls of intermediate filaments. Since a rhabdoid phenotype may be present in a wide spectrum of tumours, particularly those occurring in adults, the diagnosis of rhabdoid tumour requires exclusion of an underlying alternative line of differentiation.

ICD-O code 8963/3

Epidemiology

Malignant rhabdoid tumours are well defined and characterized entities in both the kidney and central nervous system. Due to histological overlap with other neoplasms, rhabdoid tumour as a distinct entity arising in soft tissue has taken longer to define. However, it has become apparent that these tumours, if carefully defined, are confined almost exclusively to infants and children. Congenital and even fetal cases, some with disseminated disease at the time of diagnosis, are well documented {972, 980, 2259}. An increasing number of familial cases are recognized {406, 1733}.

Sites of involvement

The tumours may arise at a variety of topographic locations, including liver,

heart and gastrointestinal system. Soft tissue lesions seem to arise most frequently in deep, axial locations, including the neck and paraspinal regions. Cutaneous lesions are well described. Imaging studies are not felt to be particularly helpful in the diagnosis of soft tissue rhabdoid tumours, other than to delineate the extent of tumour as the features are non-specific {1802}.

Macroscopy

Rhabdoid tumours have been described as primarily unencapsulated masses, generally less than 5 cm in greatest dimension. The cut surface is soft and grey to tan in colour. Foci of both haemorrhage and necrosis are frequently observed {1150}.

Histopathology

Rhabdoid tumours are densely cellular, comprised of sheets or solid trabeculae of neoplastic cells with large, vesicular, round to bean-shaped nuclei, prominent centrally located nucleoli, and abundant eccentric cytoplasm. Less common features include scattered non-neoplastic, osteoclast-like giant cells, a myxoid background, a lack of cellular cohesiveness, and increased collagen deposition between trabeculae of tumour cells. Mitoses are frequent, averaging approximately one per high power field, and necrosis is common.

The diagnostic hallmark of this tumour by routine haematoxylin and eosin staining is a distinctive, globoid, hyaline, eosino-

philic, cytoplasmic inclusion. While these distinctive cells are numerous in most tumours, occasional tumours may consist primarily of primitive, undifferentiated "small round blue cells" with only a minority of cells having a rhabdoid phenotype. In these cases, the rhabdoid cells may occur in clusters or scattered singly throughout the tumour, highlighting a potential diagnostic challenge in a small biopsy sample.

A wide variety of tumours, including some carcinomas, sarcomas, meningiomas, melanomas, lymphomas, and mesotheliomas, may display rhabdoid features, either focally or diffusely, fuelling much of the "entity vs phenotype" debate that has surrounded these tumours in the past. When present in a tumour with an otherwise documentable line of differentiation, the rhabdoid phenotype should be reflected in the diagnosis, either as a composite extrarenal rhabdoid tumour (particularly if the phenotypic appearance is mixed) or as a modifier (if the phenotype is diffuse). In addition, there are rare cases of rhabdoid tumours apparently arising in proximity to cutaneous, benign, mesenchymal lesions in neonates {764,1686}.

Immunophenotype

As a variety of tumours may express the rhabdoid phenotype, immunohistochemical stains are frequently an invaluable adjunct. The majority of rhabdoid tumours coexpress vimentin and an epithelial antigen, such as keratin, epithelial mem-



Fig. 9.68 Congenital rhabdoid tumour arising in the soft tissue of the thigh of a neonate.

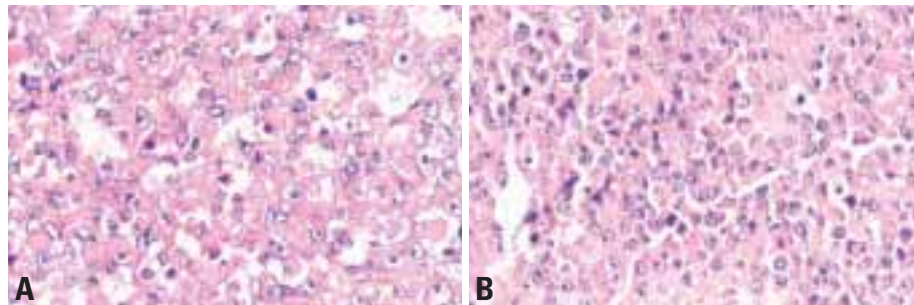


Fig. 9.69 Extrarenal rhabdoid tumour. **A** Cells contain abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. **B** Note prominent pale-pink inclusions.

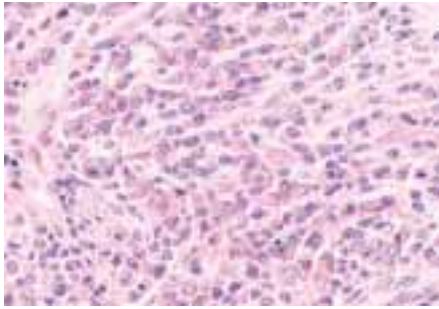


Fig. 9.70 Extrarenal rhabdoid tumour. Note diffuse, discohesive growth pattern and prominent cytoplasmic inclusions.

brane antigen and/or CAM5.2. In addition, a significant percentage of tumours frequently express neuroectodermal antigens such as CD99, synaptophysin, and/or NSE. Expression of muscle specific actin and focal S-100 positivity are also not uncommon. However, despite the frequent polyphenotypic appearance, desmin, myoglobin and CD34 are not expressed {634,1150,2141}.

Ultrastructure

The classic rhabdoid tumour cell is ultrastructurally characterized by cytoplasmic whorls of intermediate filaments measuring 8-10 nm in diameter. These filamentous whorls may incorporate mitochondria, lipid droplets or fragments of endoplasmic reticulum. A double immunofluorescence and three dimensional imaging study suggests that these whorls represent cytokeratin, while vimentin forms a filamentous network throughout the cytoplasm. In addition to the distinctive whorls, rhabdoid tumour cells, contain the usual, non-specific cadre of cytoplasmic organelles, including few mitochondria, lysosomes, free ribosomes and dilated rough endoplasmic reticulum, along with scattered lipid droplets. Variably developed intercellular attachments may be seen, but true desmosomes are not present {2137}.

Due to sampling, typical rhabdoid cells may or may not be identified in tumours with a rhabdoid phenotype, regardless of whether the lesion is a true rhabdoid tumour or otherwise. Ultrastructural examination of these tumours is probably most helpful in excluding rhabdoid tumour histology as an uncommon phenotypic pres-

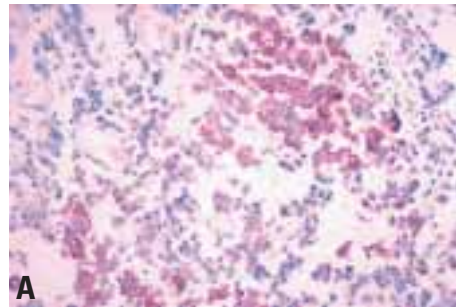
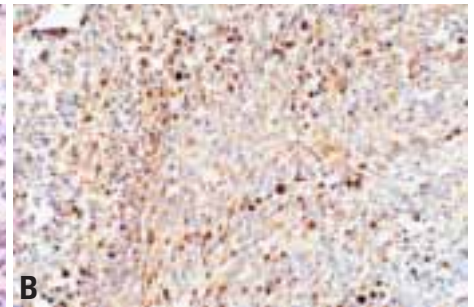


Fig. 9.71 Extrarenal rhabdoid tumour. **A** Focal positivity for epithelial membrane antigen is a frequent finding. **B** Positivity for cytokeratin AE-1/AE-3 in the cytoplasm, with accentuation of the filamentous inclusions, is commonly seen.



entation of an otherwise typical sarcoma or carcinoma of known histogenesis.

Genetics

The identification of deletions and occasional translocations (the latter involving partner chromosome regions 1p36, 6p12, 11p15 and 18q21) {881, 1548, 1689, 1813} of chromosome 22 band q11.2 in a number of soft tissue rhabdoid tumours provided the first and most convincing evidence that at least a subgroup of these tumours represented a distinct clinicopathological entity. Conversely, chromosome 22 deletions were distinctly uncommon in a limited number of composite extrarenal rhabdoid tumours studied, supporting the hypothesis that the rhabdoid phenotype was a manifestation of anaplastic progression modulated by a separate genetic mechanism {743}. Subsequent identification of mutations and homozygous deletions of the *SMARCB1* (a.k.a. *hSNF5* or *INI1*) gene in the majority of rhabdoid tumours has confirmed the initial karyotypic and molecular cytogenetic observations {192, 1921, 2201}. *SMARCB1* mutations and deletions are also characteristic of rhabdoid tumours originating in the kidney and central nervous system and have been identified in a subset of choroid plexus carcinomas, medulloblastomas, central PNETs, along with a rare glioblastoma multiforme and rhabdomyosarcoma {483, 1922}.

Although *SMARCB1* functions as a tumour suppressor gene, the mechanism of its inactivation is usually not the classic "mutation and subsequent deletion of the second normal allele." Most malig-

nant rhabdoid tumours are characterized by either a homozygous deletion or partial / complete isodisomy of chromosome 22. Homozygous deletions seem to be present in the majority of cases in which a translocation is documented {1813}. In addition to chromosome 22 rearrangements and *SMARCB1* inactivation, other chromosomal abnormalities and *TP53* mutation / overexpression have been reported in isolated soft tissue rhabdoid tumours {394,546,1052,1122,2021}.

Prognostic factors

Extrarenal rhabdoid tumours, like their renal and central nervous system counterparts, are characterized by aggressive biological behaviour. Regardless of therapy and current identifiable tumour or patient-specific features, survival rates are dismal.

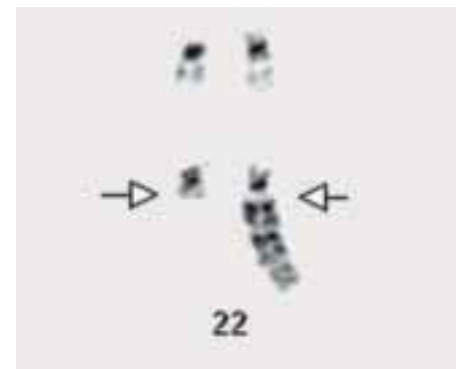


Fig. 9.72 Partial karyotype illustrating homozygous loss of the *SMARCB1* locus on 22q. One homologue (left) is deleted, and the other (right) is involved in an unbalanced translocation. Arrows indicate break-points. For comparison, two normal copies of chromosome 22 are shown (top).

Neoplasms with perivascular epithelioid cell differentiation (PEComas)

A.L. Folpe

Definition

Neoplasms with **p**erivascular **e**pithelioid **c**ell differentiation (PEComas) are mesenchymal tumours composed of histologically and immunohistochemically distinctive perivascular epithelioid cells. The PEComa family of tumours includes angiomyolipoma (AML), clear cell "sugar" tumour of the lung (CCST), lymphangiomyomatosis (LAM), clear cell myomelanocytic tumour of the falciform ligament / ligamentum teres (CCMMT) and unusual clear cell tumours of the pancreas, rectum, abdominal serosa, uterus, vulva, thigh, and heart. Some of these lesions are discussed in the WHO Classification of renal (AML), hepatic (AML) and pulmonary (CCST, LAM) tumours.

Synonyms

Extrapulmonary sugar tumour, perivascular epithelioid cell tumour (PECT), monotypic epithelioid angiomyolipoma.

Epidemiology

PEComas other than AML, CCST or LAM are exceedingly rare. Approximately 31 PEComas other than AML, LAM or CCST have been reported {225,417,698,701,802,1441,1676,2084,2100,2186,2335}.

CCMMT usually occurs in young girls, with a mean age at diagnosis of 11

years {698,2084}. Uterine PEComas have a mean age at diagnosis of 54 years {417,1441,1821,2186}. Almost all other reported PEComas have been in women, with a wide age range {225,802,2100}.

Sites of involvement

PEComas have been reported in the uterus (13 cases), falciform ligament (8 cases), large and small bowel (3 cases), pancreas (1 case), pelvic sidewall (1 case), vulva (1 case), thigh (1 case) and heart (1 case) {225,417,698,701,802,1441,1676,2084,2100,2186,2335}.

Clinical features

CCMMT presents as a painful abdominal mass. Uterine PEComas may present with vaginal bleeding. Other PEComas typically present as a painless mass. No association with tuberous sclerosis complex has been demonstrated in non-AML, CCST or LAM PEComas.

Histopathology

Perivascular epithelioid cells (PECs) are characterized by perivascular location, often with a radial arrangement of cells around the vascular lumen {227,1675}. Typically, PECs in an immediate perivascular location are most epithe-

lioid and spindled cells resembling smooth muscle are seen away from vessels. Great variation is seen in the relative proportion of epithelioid and spindled cells. PECs have clear to granular, lightly eosinophilic cytoplasm, rather than the dense eosinophilia of true smooth muscle cells. They typically display small, centrally placed, normochromatic, round to oval nuclei with small nucleoli, although striking hyperchromasia and nuclear irregularity may be present.

The majority of PEComas resemble CCST, with PEC arrayed around thin-walled blood vessels {2100,2186,2335}. However, a significant percentage of reported PEComas display striking nuclear atypia, elevated mitotic activity and necrosis {225,1786,2100}. Uterine PEComas may show an infiltrative growth pattern similar to that of low grade endometrial stromal sarcoma {2186}. CCMMT differs somewhat from other PEComas in that it is almost exclusively a spindle cell lesion, with uniform moderately sized cells arranged in fascicles and nests {698,701,2084}. A striking feature is the elaborate vasculature, with small arcing vessels that subdivide the tumour into coarse packets, reminiscent of renal cell carcinoma. Mitotic activity, angiolymphatic invasion and necrosis have not been reported.

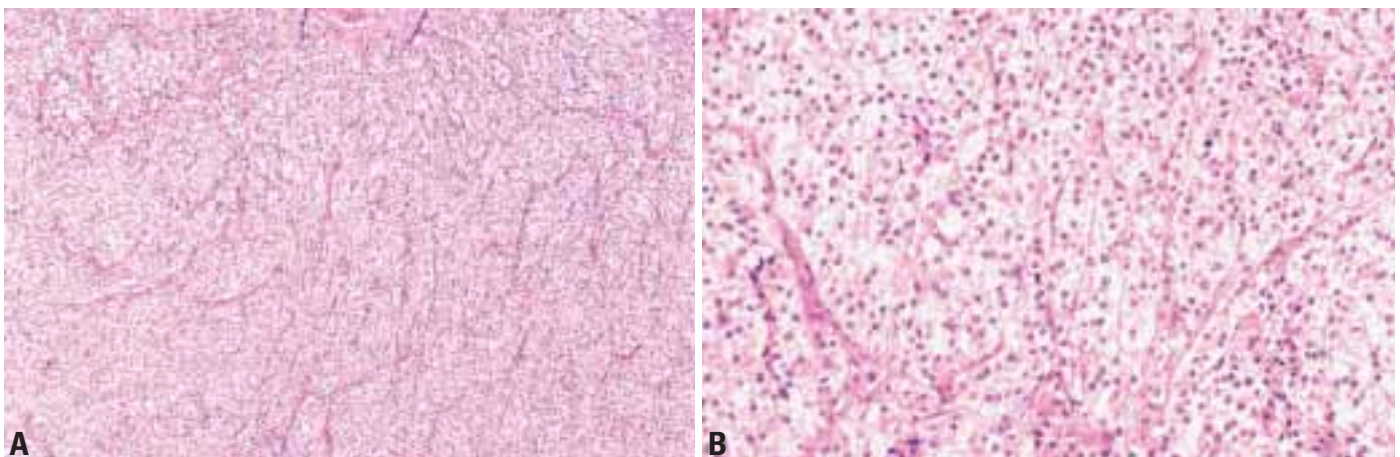


Fig. 9.73 PEComa. **A** Note the typical nested architecture. **B** In many cases, tumour cells have a clear cytoplasm, reminiscent of clear cell carcinoma.

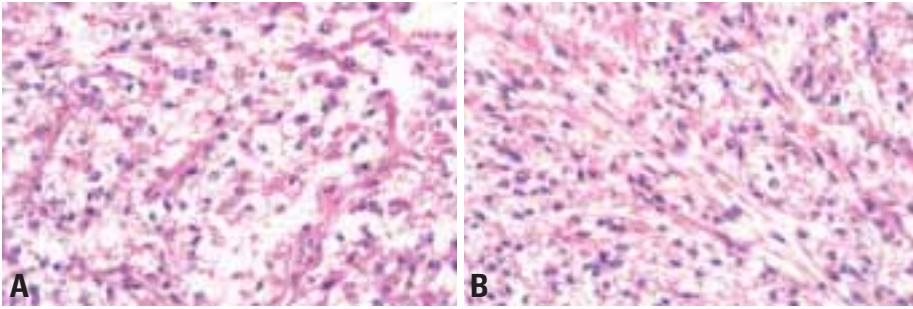


Fig. 9.74 **A** Epithelioid cytomorphology in a PEComa. **B** PEComa consisting of clear to lightly eosinophilic spindle cells.

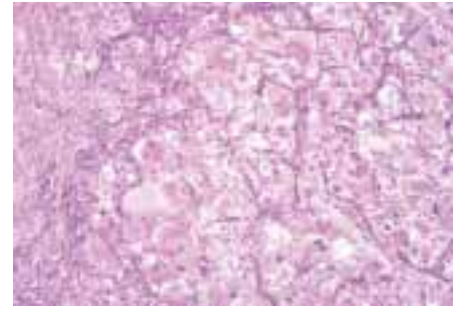


Fig. 9.76 Some PEComa cases show marked cytological pleomorphism.

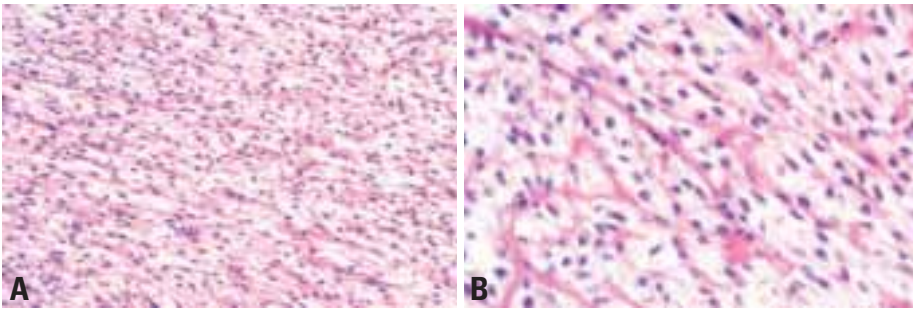


Fig. 9.75 **A** PEComa showing fascicular arrangement and delicate, arborizing capillaries. **B** High power view of a PEComa with round nuclei with small nucleoli.



Fig. 9.77 PEComas are consistently immunoreactive for HMB45.

Immunohistochemistry

The PEC is characterized by positivity with melanocytic markers, such as HMB-45, Melan-A, tyrosinase, microphthalmia transcription factor, and NKI/C3 and muscle markers, such as smooth muscle actin, pan-muscle actin, muscle myosin and calponin {225, 226, 288, 329, 698, 1199, 1674, 2034, 2100, 2224, 2339}. Desmin is less often positive and cytokeratin and S100 protein are usually absent. In PEComas, the most sensitive melanocytic markers are HMB-45, Melan-A and microphthalmia transcription factor {2034, 2339}.

Ultrastructure

Ultrastructural studies have documented abundant cytoplasmic glycogen, pre-melanosomes, thin filaments with occasional dense bodies, hemidesmosomes and poorly formed intercellular junctions {698, 2084, 2100}.

Genetics

The presence of a $t(3;10)(?p13;?q23)$ has been reported in one CCMMT {698}. Other PEComas have not been studied by cytogenetic or molecular genetic methods. A small number of CCMMT have also been shown to lack expression of the tuberous sclerosis-associated *TSC2* gene product tuberlin {698}.

Prognostic factors

Clear criteria for malignancy in PEComas have not been elaborated, owing to their rarity. Development of such criteria has also been complicated by the relatively frequent presence of pseudomalignant changes in the most common PEComa, AML. However, clinically malignant (i.e., metastatic) AML, usually of the epithelioid type, have been convincingly documented, and these tumours closely resemble many

reported PEComas of non-AML, LAM or CCST type {1199, 1339, 1673, 1744, 1786, 2323}. Sarcomas arising in pre-existing benign AML have also been reported {356, 655}. Furthermore, clinically malignant pulmonary CCST have been reported {752}. Clinically malignant PEComas of the bowel, uterus, and heart have been reported {225, 2100}. On the basis of these prior reports, it appears that PEComas displaying any combination of infiltrative growth, marked hypercellularity, nuclear enlargement and hyperchromasia, high mitotic activity, atypical mitotic figures, and coagulative necrosis should be regarded as malignant. Malignant PEComas are aggressive sarcomas that frequently result in the death of affected patients. In contrast to other forms of PEComa, CCMMT to date appears relatively benign.

Intimal sarcoma

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Definition

Intimal sarcomas are malignant mesenchymal tumours arising in large arterial blood vessels of the systemic and pulmonary circulation. The defining feature is the predominant intraluminal growth with obstruction of the lumen of the vessel of origin and the seeding of emboli to peripheral organs.

ICD-O code 8800/3

Epidemiology

Intimal sarcomas are very rare tumours [219, 286]. According to the published case reports pulmonary intimal sarcomas are almost twice as common as tumours of aortic origin (165 versus 100 reported patients) [219, 286, 772, 1916]. Pulmonary intimal sarcomas show a slight female predominance (female to male ratio of about 1.3), while no sex predilection could be observed for aortic tumours. Intimal sarcomas are tumours of adulthood with a broad age range. The mean age at the time of diagnosis is 48 years for pulmonary and 62 years for aortic intimal sarcoma [286].

Sites of involvement

Intimal sarcomas of the pulmonary circulation mainly involve the proximal vessels and are frequently located in the pulmonary trunk (80%), the right or left main pulmonary arteries (50-70%), or both (40%) [286, 287, 1577]. Some tumours also involve the pulmonary valve or

extend into the right ventricular outflow tract. Direct infiltration or lung metastases are observed in 40% of affected patients while extrathoracic spread occurs in about 20% of cases, involving the lungs, kidneys, lymph nodes, the brain and skin [286, 1577].

Aortic intimal sarcomas mostly arise in the abdominal aorta between the celiac artery and the iliac bifurcation and approximately 30% of tumours are located in the descending thoracic aorta. Arterial embolic tumour dissemination in these patients is frequent and results in distant metastases involving bone, peritoneum, liver and mesenteric lymph nodes [286, 1861].

Clinical features

The clinical presentation of intimal sarcomas is often unspecific and related to tumour emboli. Due to rarity of this tumour, proper diagnosis is often delayed or made post mortem. In pulmonary intimal sarcomas recurrent pulmonary embolic disease is the most common primary diagnosis. Intimal sarcomas of the aorta most commonly present with consequences of embolic incidents such as claudication and absent pulses of lower extremities, back pain and abdominal angina resulting from mesenteric artery occlusion, malignant hypertension or rupture of aneurysm formed by the tumour [1572].

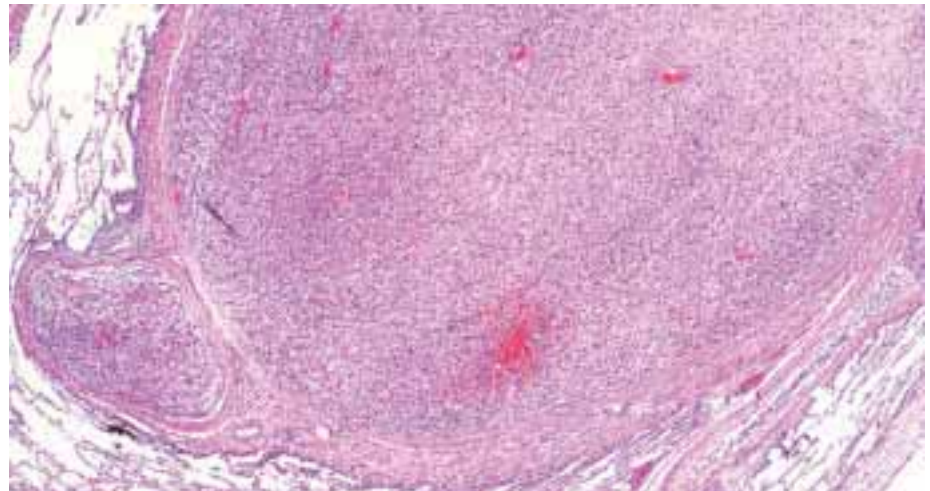


Fig. 9.79 Intimal sarcoma. Spreading of the tumour along the intrapulmonary branches of the pulmonary artery (from B. Bode-Lesniewska et al. [219]).



Fig. 9.78 Intimal sarcoma. **A** Chest CT of a patient with an intimal sarcoma of the left pulmonary artery. **B** View of the hilum of the resected lung of this patient with obstruction of the lumen of the pulmonary artery by tumour tissue. **C** Endarterectomy specimen of another patient with intimal sarcoma of the pulmonary artery (from B. Bode-Lesniewska et al. [219]).

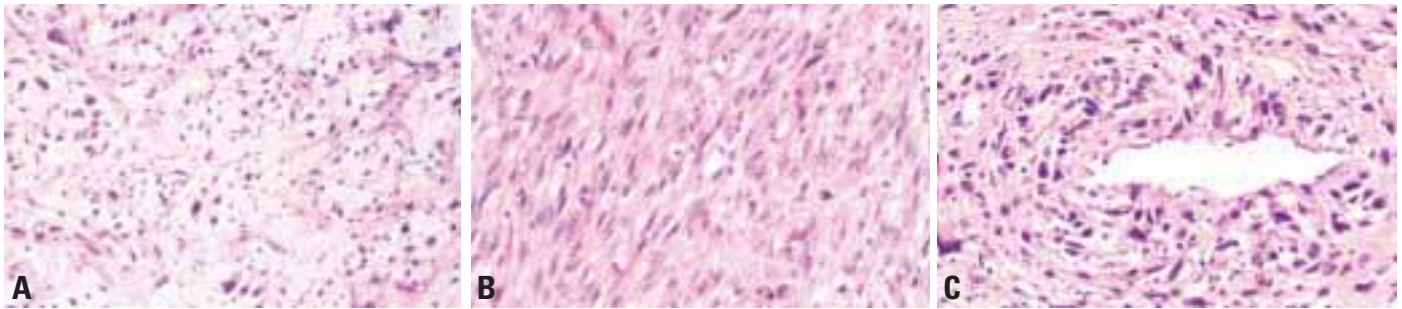


Fig. 9.80 Intimal sarcoma. **A** Myxoid tumour with low cellular density. **B** Bundles of tumour cells resembling leiomyosarcoma. **C** An endothelially lined vascular cleft surrounded by pleomorphic tumour cells (from B. Bode-Lesniewska et al. [219]).

The conventional imaging methods are often disappointingly non-specific, but the neoplastic nature of the tissue occluding the lumen can be suspected in modern diagnostic procedures (CT, MRI, PET) [1745, 2112].

Macroscopy

Intimal sarcomas are by definition mostly intravascular polypoid masses attached to the vessel wall and grossly resembling thrombi. They may extend distally along the branches of the involved vessels. Occasionally a mucoid lumen cast can be recovered intraoperatively. Some of the aortic tumours may cause thinning and aneurysmal dilatation of the vessel wall with adherent thrombotic material suggesting atherosclerotic changes, particularly in the abdominal aorta. Some of these lesions of the pulmonary arteries may have harder, bony areas corresponding to osteosarcomatous differentiation.

Histopathology

Intimal sarcomas are usually poorly differentiated mesenchymal malignant tumours of fibroblastic or myofibroblastic differentiation, consisting of mildly to severely atypical spindle cells with varying degrees of atypia, mitotic activity, necrosis and nuclear polymorphism. Some tumours show large myxoid areas or epithelioid appearance of tumour cells [804, 974]. Prominent spindling and bundling of the tumour cells may resemble leiomyosarcoma. Rare cases may contain areas of rhabdomyo-, angio- or osteosarcomatous differentiation [286, 287, 804, 974, 1577]. Aortic intimal sarcomas – unlike pulmonary ones – uncommonly contain areas of specific differentiation other than a myofibroblastic one, although some tumours with angio- and rhabdomyosarcomatous appearance have been described in case reports [1466, 1861].

Immunophenotype

The undifferentiated tumour cells of intimal sarcomas usually exhibit immunoreactivity for vimentin and osteopontin [771]. Variable positivity for smooth muscle actin has been observed and few tumours exhibit some positive staining with antibodies against desmin. In a typical case of intimal sarcoma the vascular markers (CD31, CD34 and FVIII) are negative, but may be positive in areas with angiosarcomatous differentiation.

Ultrastructure

Ultrastructurally, microfilaments, dense bodies, as well as a discontinuous external lamina can be found in intimal sarcomas as features compatible with myofibroblastic differentiation [286, 1039]. In tumours with rhabdomyosarcomatous differentiation some rudimentary sarcomeric structures may be observed [1466].

Genetics

In a recent study using comparative genomic hybridization (CGH), gains and amplifications of the 12q13-14 region were identified in 6/8 tumours. Other, less consistent alterations were losses on 3p, 3q, 4q, 9p, 11q, 13q, Xp and Xq, gains on 7p, 17p and 17q as well as amplifications on 4q, 5p, 6p and 11q [219].

Prognostic factors

The prognosis of intimal sarcomas originating both in the aorta and in pulmonary arteries is poor with mean survival times of about 5-9 months in patients with aortic tumours and of 13-18 months in patients with pulmonary sarcomas [1916]. Surgical and adjuvant therapy may prolong survival without influencing the generally poor outcome [219, 286, 1577].



Fig. 9.81 CGH analysis of 8 intimal pulmonary artery sarcomas. Bars to the left of the chromosomes correspond to losses, bars to the right, to gains; thick bars correspond to amplifications of genetic material (from B. Bode-Lesniewska et al. [219]).