



CHAPTER 2

Fibroblastic / Myofibroblastic Tumours

Fibroblastic / myofibroblastic tumours represent a very large subset of mesenchymal tumours. Many lesions in this category contain cells with both fibroblastic and myofibroblastic features, which may in fact represent functional variants of a single cell type. The relative proportions of these cell types vary not only between individual cases but also within a single lesion over time (often in proportion to cellularity). A significant subset of spindle cell and pleomorphic sarcomas are probably myofibroblastic in type but, to date, only low grade forms have been reproducibly characterized. Among lesions formerly known as malignant fibrous histiocytoma (MFH – see Chapter 3), at least some represent pleomorphic myofibrosarcomas.

Principal changes and advances since the 1994 WHO classification have been the characterization of numerous previously undefined lesions, including ischaemic fasciitis, desmoplastic fibroblastoma, mammary-type myofibroblastoma, angiomyofibroblastoma, cellular angiofibroma, Gardner fibroma, low grade fibromyxoid sarcoma, acral myxoinflammatory fibroblastic sarcoma, sclerosing epithelioid fibrosarcoma and low grade myofibroblastic sarcoma.

Conceptual changes have included the clearer recognition of solitary fibrous tumour in soft tissue and the realization that most cases of so-called haemangiopericytoma belong in this category, as well as the reclassification of lesions formerly labelled myxoid MFH as myxofibrosarcoma and the definitive allocation of these tumours to the fibroblastic category.

Nodular fasciitis

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Definition

Nodular fasciitis is a mass-forming fibrous proliferation that usually occurs in the subcutaneous tissue. It is composed of plump but uniform fibroblastic / myofibroblastic cells and typically displays a loose or tissue culture-like growth pattern. Intravascular fasciitis and cranial fasciitis are histologically similar lesions that extend into vessel lumens and involve the skull and overlying soft tissue, respectively.

Synonym

Pseudosarcomatous fasciitis.

Epidemiology

Nodular fasciitis is comparatively common among soft tissue mass lesions {39, 173, 985, 1136, 1156, 1399, 1727, 1940, 2000}. It occurs in all age groups but more often in young adults. Intravascular fasciitis {1727} and cranial fasciitis {1225} are rare. Intravascular fasciitis is found mostly in persons under 30 years of age, whereas cranial fasciitis develops predominantly in infants under 2 years of age. There is no sex predilection for nodular fasciitis or intravascular fasciitis, but cranial fasciitis is more frequent in boys.

Sites of involvement

Nodular fasciitis is usually subcutaneous, although occasional cases are intramuscular. Dermal localization is very rare {812} (see volume on skin tumours). Any part of the body can be involved, but the upper extremity, trunk, and head and neck are most frequently affected. Intravascular fasciitis is also chiefly subcutaneous. It occurs in small to medium-sized vessels, predominantly veins but occasionally arteries (or both). Cranial fasciitis typically involves the outer table of the skull and contiguous soft tissue of the scalp, and may extend downward through the inner table into the meninges.

Clinical features

Nodular fasciitis typically grows rapidly and has a preoperative duration in most,

but not all, cases of not more than 1-2 months. Soreness or tenderness may be present. It usually measures 2 cm or less and almost always less than 5 cm. Intravascular fasciitis may enlarge more slowly but is also normally not more than 2 cm in size. Cranial fasciitis expands quickly, like nodular fasciitis, and may become somewhat larger than the usual example of the latter. When the skull is involved, X-ray shows a lytic defect, often with a sclerotic rim. By contrast, nodular fasciitis presents as a nondistinctive soft-tissue mass on imaging studies, and there is little information on imaging of intravascular fasciitis.

Aetiology

Some patients with nodular fasciitis report trauma to the site of the lesion, but the majority do not. Birth trauma may be a factor in the genesis of cranial fasciitis.

Macroscopy

Grossly, nodular fasciitis may appear circumscribed or infiltrative but is not encapsulated. The cut surface varies from myxoid to fibrous, and occasionally there is central cystic change. Intravascular fasciitis ranges from nodular to plexiform, the latter contour resulting when there is extensive intravascular growth. Cranial fasciitis is typically cir-

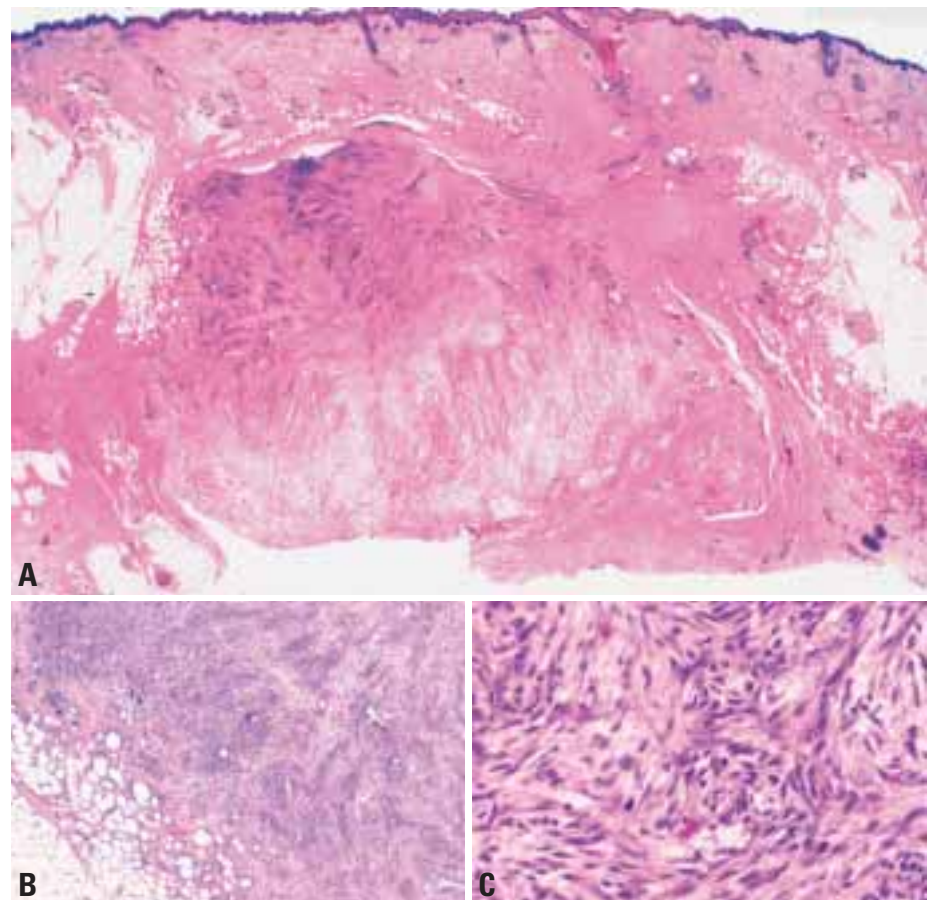


Fig. 2.01 Nodular fasciitis. **A** This low power view illustrates the typical subcutaneous location. **B** Detail from the same lesion showing infiltration of adjacent fat. **C** This high power view shows the typical plump but regular fibroblasts / myofibroblasts (From R. Kempson et al. {1086}).

cumscribed and rubbery to firm, and may be focally myxoid or cystic in its centre.

Histopathology

Nodular fasciitis is composed of plump but regular spindle-shaped fibroblasts (or myofibroblasts) lacking nuclear hyperchromasia and pleomorphism. Mitotic figures may be plentiful, but atypical mitoses would not be expected. The lesion may be highly cellular, but typically it is at least partly loose appearing and myxoid, with a torn, feathery, or tissue culture-like character. In more cellular areas, there is often growth in S- or C-shaped fascicles, and sometimes a storiform pattern. There is normally little collagen, but this may be increased focally, and keloidlike collagen bundles may be present and even occasionally prominent. Isolated cases may show extensive stromal hyalinization. Extravasated red cells, chronic inflammatory cells, and multinucleated osteoclastlike giant cells are other frequently identified features. The lesional border is typically, at least focally, infiltrative, although it may be well delineated; peripheral extension is often seen between fat cells in the subcutis and between muscle cells in intramuscular locations. Small vessels are numerous in some examples, resulting in a resemblance to granulation tissue, sometimes with poorly delimited margins. Intravascular fasciitis and cranial fasciitis are basically similar to nodular fasciitis histologically, although the former often displays a greater number of osteoclastlike giant cells. Intravascular fasciitis ranges from predominantly extravascular, with only a minor intravascular component, to predominantly intravascular. Osseous metaplasia is occasionally seen in nodular fasciitis (fasciitis ossificans) {450,1193} and cranial fasciitis.

Immunophenotype

Stains for SMA and MSA are usually positive, but desmin positivity is rare {1497}. These results are consistent with myofibroblastic differentiation but do not distinguish nodular fasciitis from many other

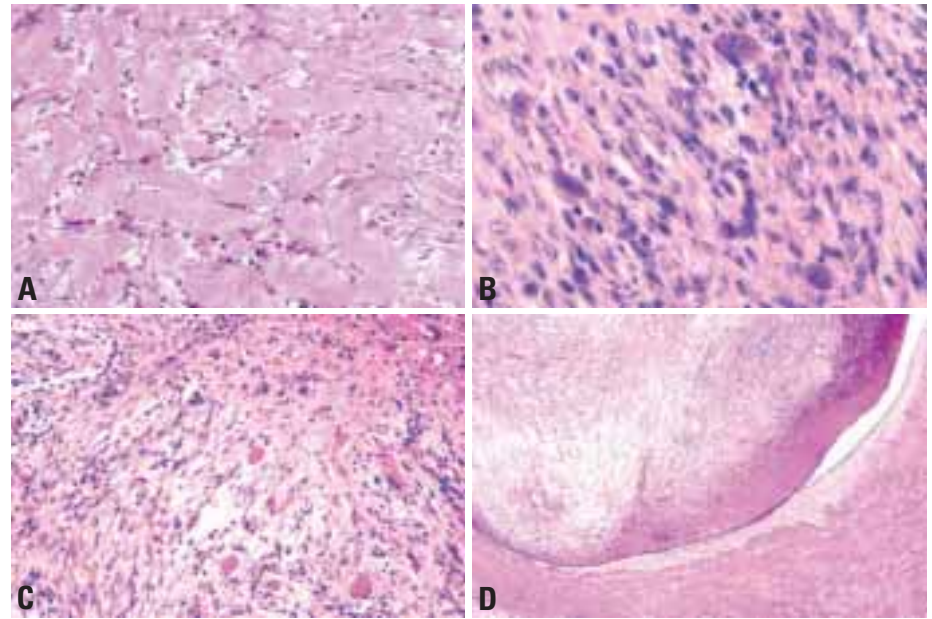


Fig. 2.02 Nodular fasciitis. **A** Note the thick, keloidlike collagen bundles. **B** Multinucleated, osteoclastlike giant cells are sometimes present. **C** Nodular fasciitis, intramuscular variant. There is a loose and "torn" appearance, but greater fibrosis than usual in one area (upper right). **D** Intravascular fasciitis. The intravascular location is demonstrated at scanning magnification (From R. Kempson et al. {1086}).

mesenchymal proliferations. CD68 staining is present in the osteoclast-like giant cells and occasionally in spindle cells. Keratin and S100 protein are typically negative.

Ultrastructure

By electron microscopy, nodular fasciitis demonstrates fibroblastic/myofibroblastic features; the cells are elongated, have abundant, often dilated rough endoplasmic reticulum, and sometimes demonstrate cytoplasmic filaments with dense bodies, pinocytotic vesicles, and cell junctions. Like the immunohistochemical profile, these findings are common to numerous mesenchymal entities.

Genetics

Assessment of DNA ploidy in nodular fasciitis using flow cytometry has shown these lesions to be diploid {575,1621}. In contrast, clonal chromosomal abnormalities have been detected by cytogenetic analysis in three cases of nodular fasciitis including a rearrangement of 3q21 with a group D acrocentric chromosome

in two {1869,2229}. The remaining case, a case of nodular fasciitis arising in the breast, exhibited a 2;15 translocation, loss of chromosomes 2 and 13, and several marker chromosomes {199}. Although the observation of clonality in these limited cases of nodular fasciitis would appear to support true neoplastic rather than reactive origin, it is possible that the culturing conditions used may favour growth of a particular clone or type of cell.

Prognostic factors

Recurrence of nodular fasciitis after excision is very rare. It has been observed occasionally (<2% of cases) after incomplete excision of *bona fide* examples, but in general recurrence should prompt reevaluation of the diagnosis. Metastasis does not occur. Intravascular fasciitis has the same innocent behaviour as nodular fasciitis, despite its sometimes prominent intravascular growth, as does cranial fasciitis.

Proliferative fasciitis and proliferative myositis

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Definition

Proliferative fasciitis is a mass-forming subcutaneous proliferation characterized by large ganglion-like cells in addition to plump fibroblastic / myofibroblastic cells similar to those seen in nodular fasciitis. Proliferative myositis has the same cellular composition but occurs within skeletal muscle.

Epidemiology

Proliferative fasciitis and myositis are much less common than nodular fasciitis. Both occur predominantly in middle-aged or older adults {349,594,1093}, i.e., an older age group than for nodular fasciitis. A rare variant of proliferative fasciitis is described in children {1395}.

Site of involvement

Proliferative fasciitis develops most frequently in the upper extremity, particularly the forearm, followed by the lower extremity and trunk. Proliferative myositis arises predominantly in the trunk, shoulder girdle, and upper arm and less often in the thigh. By definition, proliferative fasciitis is subcutaneous and proliferative myositis is intramuscular.

Clinical features

Both proliferative fasciitis and proliferative myositis characteristically grow rap-

idly and are usually excised within 2 months of the time they are first noted. Proliferative fasciitis almost always measures less than 5 cm and is most often less than 3 cm. Proliferative myositis may be slightly larger but not greatly so. Either lesion may be painful or tender, but this is more common with proliferative fasciitis. There is not much experience with imaging of these conditions.

Aetiology

There is sometimes a history of trauma to the site of proliferative fasciitis and myositis, but more often there is not.

Macroscopy

Proliferative fasciitis typically forms a poorly circumscribed mass in the subcutaneous tissue and may extend horizontally along fascia. The rare childhood variant is often better circumscribed. Proliferative myositis is also poorly marginated and replaces a variable proportion of the involved muscle.

Histopathology

Both proliferative fasciitis and myositis contain plump fibroblastic/myofibroblastic spindle cells similar to those seen in nodular fasciitis but also demonstrate large cells with rounded nuclei, prominent nucleoli, and abundant amphophilic

to basophilic cytoplasm. These features result in a resemblance to ganglion cells, and the cells are often described as ganglion-like. They usually have one nucleus but may have two or three. They vary in number in different examples and may be evenly or patchily distributed. Mitotic figures are found in both the spindle cells and ganglion-like cells and may be relatively numerous, but are not atypical. The stroma varies from myxoid to collagenous, and the lesional borders are typically infiltrative or even ill defined. Proliferative fasciitis may grow laterally along fascial planes, whereas proliferative myositis extends between individual muscle fibres and small groups, creating the characteristic "checkerboard" pattern. The childhood variant of proliferative fasciitis normally has better delineated borders than the adult form, greater cellularity, dominance of ganglion-like cells and more mitoses. Focal necrosis and acute inflammation may be present, in addition. Proliferative myositis may contain metaplastic bone, thus demonstrating kinship to myositis ossificans.

Immunophenotype

The immunohistochemical profile of proliferative fasciitis and myositis is similar to that of nodular fasciitis, with usual positivity for SMA and MSA and negativity for

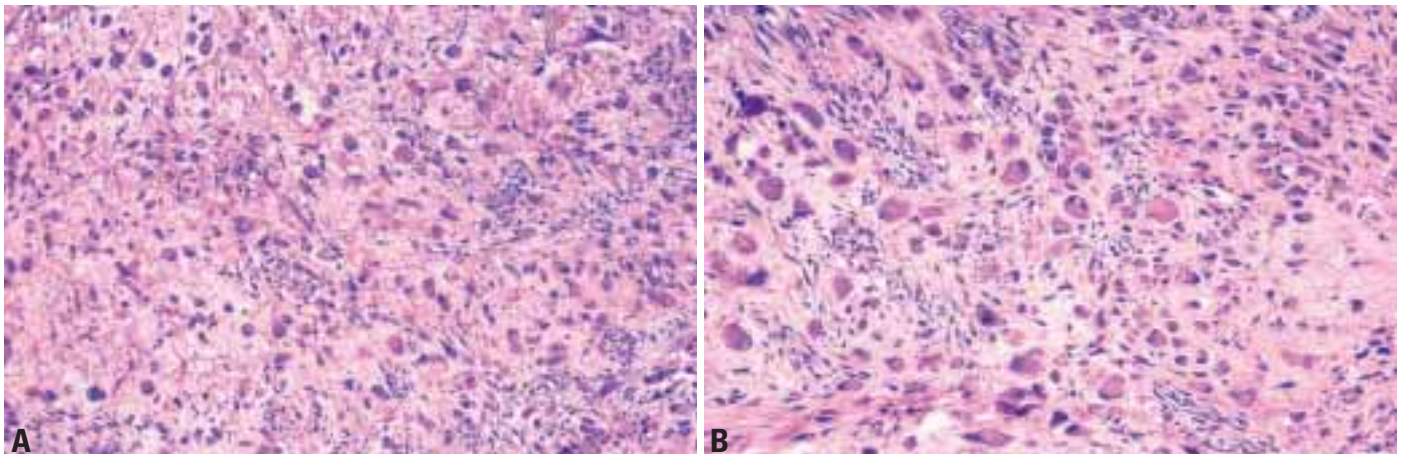


Fig. 2.03 Proliferative fasciitis. **A** In this example the ganglion-like cells are larger and more prominent. **B** On high power the details of the ganglion-like cells are better seen. (From R. Kempson et al. {1086}).

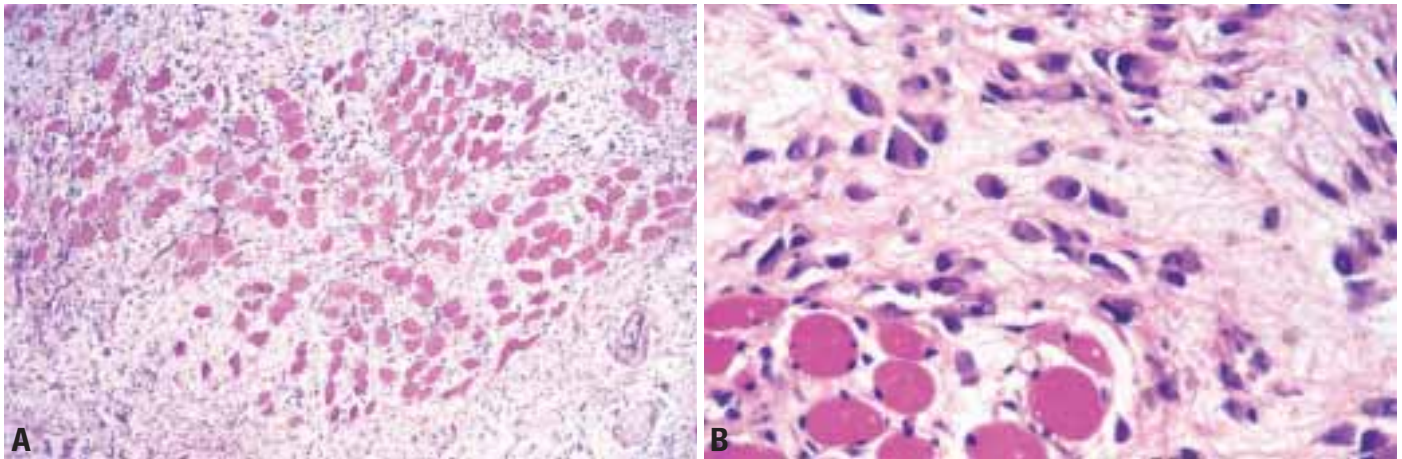


Fig. 2.04 Proliferative myositis. **A** Low power demonstrates the "checkerboard" pattern resulting from separation of muscle cells by the lesion. **B** Note the large nuclei and abundant amphophilic cytoplasm of the ganglion-like cells (From R. Kempson et al. {1086}).

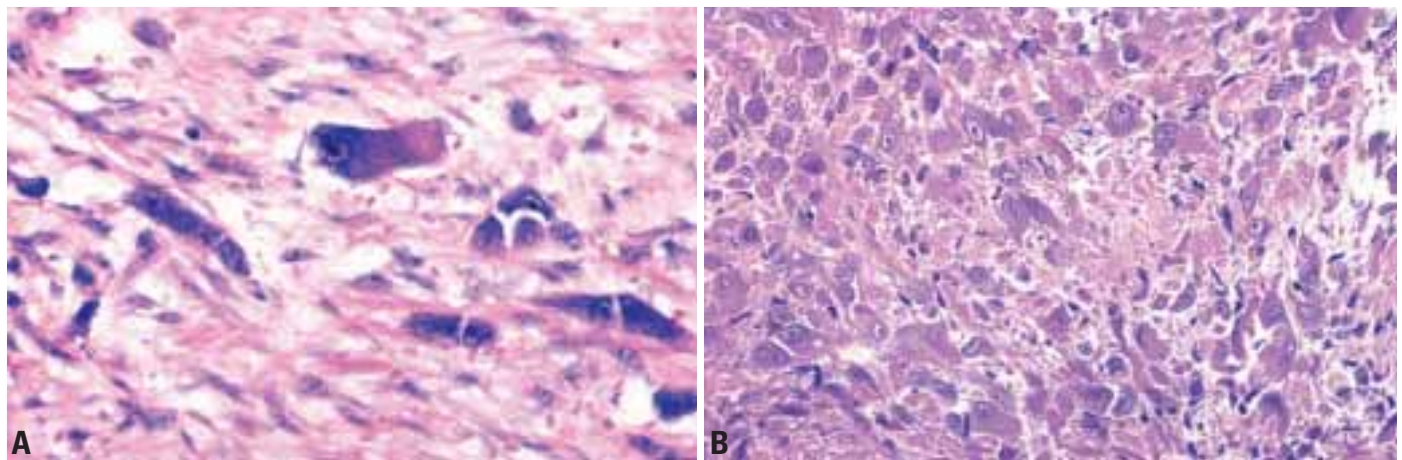


Fig. 2.05 **A** Proliferative myositis, showing in detail the cytological features of the ganglion-like cells (From R. Kempson et al. {1086}). **B** Proliferative fasciitis in childhood. Such lesions may readily be mistaken for rhabdomyosarcoma.

desmin {574,1295}. The ganglion-like cells, however, may stain only focally or weakly for actins. CD68 may stain some cells, but keratin and S100 protein are typically negative.

Ultrastructure

As with nodular fasciitis, the ultrastructural features of proliferative fasciitis and myositis are those of fibroblasts and myofibroblasts {574,1295}. The ganglion-like cells demonstrate abundant and dilated rough endoplasmic reticulum and lack neuronal characteristics.

Genetics

DNA flow cytometric analyses of proliferative fasciitis have revealed a uniformly diploid pattern {574,1295}. Trisomy 2 has been detected in a single case of proliferative fasciitis by standard cytogenetic evaluation {499}.

Cytogenetic studies of two cases of proliferative myositis have revealed distinct abnormalities {1371,1597}. An extra copy of chromosome 2 or trisomy 2 was detected in one case arising in the axilla of a 62-year-old male {1597}. The second case, arising in the rectus muscle of a

60-year-old female, showed the following translocation: t(6;14)(q23;q32) {1371}. Fluorescence in situ hybridization studies performed on uncultured cells of this latter case excluded the presence of trisomy 2.

Prognostic factors

Both proliferative fasciitis and myositis recur only rarely after local excision and do not metastasize.

Myositis ossificans and fibroosseous pseudotumour of digits

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Definition

Myositis ossificans (MO) and fibroosseous pseudotumour of digits (FP) are localized, self-limiting, reparative lesions that are composed of reactive hypercellular fibrous tissue and bone. Morphologically similar lesions may also occur in the subcutis, tendons or fascia and have been termed panniculitis ossificans and fasciitis ossificans, respectively. The rapid growth of these lesions that frequently arouses clinical suspicion in conjunction with their hypercellularity, cytological atypia, and mitotic activity makes them classic pseudosarcomas of soft tissues.

Synonyms

Pseudomalignant osseous tumour of soft tissue, extraosseous localized, nonneoplastic bone and cartilage formation, myositis ossificans circumscripta, myositis ossificans traumatica.

Epidemiology

MO and FP have a broad age distribution ranging from infancy to late adulthood (14 mos-95 years), however, they are characteristically encountered during young adulthood (mean age 32 years), and rarely occur in infants or the elderly {2,13,358,1588,2054}. Males are affected more frequently than females (3:2), however, females are more commonly involved in FP {559}. Patients with MO are typically physically active.



Fig. 2.06 Fibroosseous pseudotumour of digits presenting as a red and swollen mass.

Sites of involvement

MO may develop anywhere in the body including the extremities, trunk, and head and neck {2,805,1580,2054}. The most common locations are those most susceptible to trauma such as the elbow, thigh, buttock, and shoulder. MO-like lesions have also been reported in the mesentery {2277}. FP usually affects the subcutaneous tissues of the proximal phalanx of the fingers and less frequently the toes {559}.

Clinical features

The clinical and radiographic findings of MO parallel the stage of development of the lesion. In the early phase (1-2 weeks), the involved area is swollen and painful. Similarly, in FP the digit hurts and there is a localized fusiform swelling of the affected area.

Plain X-rays and CT scans of MO may demonstrate soft tissue fullness and oedema, whereas MRI reveals signal heterogeneity and high signal intensity on T2 weighted images {805,1169,1580,1949,2277}. Two to six weeks after the onset of symptoms, flocculent dense calcifications become evident in the periphery of the mass and eventually produce a lacy pattern of bone deposition that sharply demarcates the periphery of the lesion in an eggshell-like fashion. In FP the lesional calcification has a more random distribution. In MO this correlates with the clinical progression for the affected site becomes more circumscribed and firm and eventually evolves into a painless, hard, well-demarcated mass. After a prolonged period of time the mass may remain stable or undergo partial or complete resorption. In older stable lesions MRI exhibits a well defined mass that possesses a rim of low signal intensity (mineralized bone) and contains intralesional regions of higher intensity representing marrow fat.

Aetiology

Soft tissue injury produced by a variety of mechanisms is believed to be the initiating event in most instances and a clear

history of trauma is documented in 60-75% of cases {1580,1667}. In patients without a history of trauma, repetitive small mechanical injuries, ischaemia or inflammation have been implicated as possible causative factors. Initiation of the process is followed by proliferation of mesenchymal stem cells that produce activated fibroblasts and osteoblasts that grow in a centripetal fashion. The mechanisms underlying the characteristic pattern of zonation have not been clearly elucidated.

Macroscopy

Myositis ossificans manifests as a well delineated ovoid tan mass with a soft

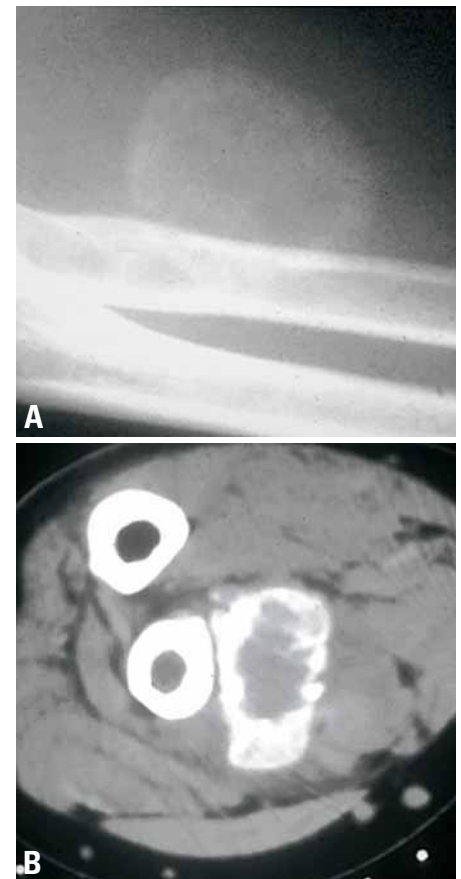


Fig. 2.07 Myositis ossificans. **A** Plain X-ray and **(B)** cross sectional CT of a forearm lesion of approximately 6 weeks duration with a well circumscribed, ossified periphery and a more lucent centre.

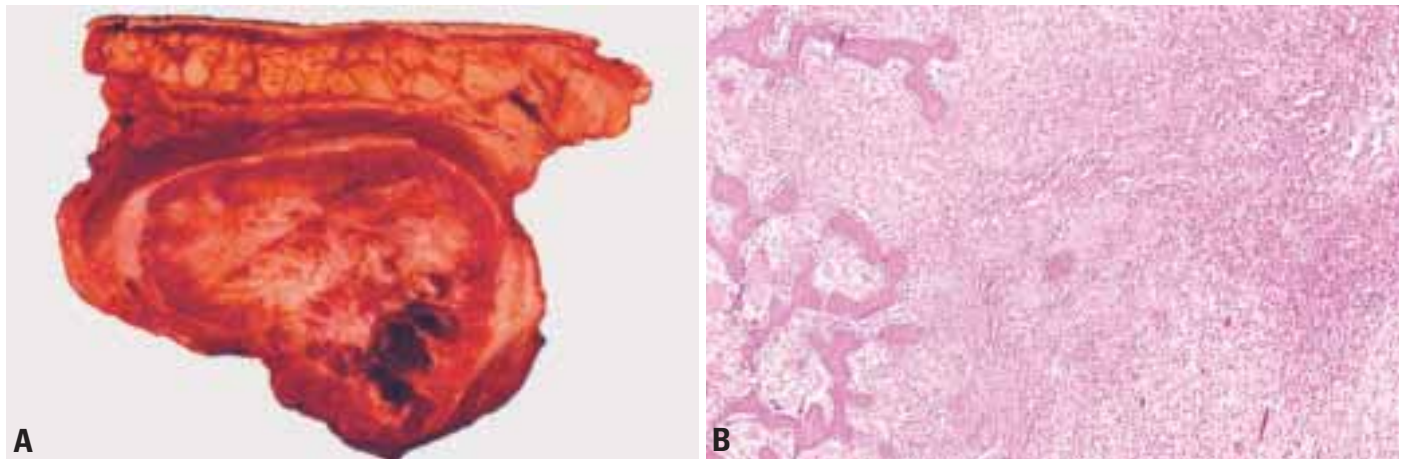


Fig. 2.08 Myositis ossificans. **A** Gross appearance of myositis ossificans in a young adult male. **B** Low power view showing typical zonation with fasciitis-like features (centre right), immature osteoid (centre) and bone formation at the periphery (left).

glistening centre and a firm, grey-white gritty periphery. The lesion ranges in size from 2-12 cm but most are approximately 5 cm in greatest dimension.

Histopathology

Myositis ossificans is characterized by a zonal proliferation of fibroblasts and bone-forming osteoblastic elements that progresses through various stages over time [1210]. In the early stages of development MO is most cellular, bearing a resemblance to nodular fasciitis, and is composed of numerous proliferating fibroblasts that are oriented randomly or in short intersecting fascicles. The fibroblasts have ill defined, tapering cell processes that consist of faintly eosinophilic cytoplasm and contain vesicular or finely granular nuclei with smooth nuclear membranes and nucleoli of variable size. Numerous mitoses may be present but atypical mitotic figures are uniformly absent. The stroma is richly vascular, oedematous or myxoid and

contains fibrin, clusters of extravasated red blood cells, scattered chronic inflammatory cells, osteoclast-like giant cells and injured or atrophic myocytes. Peripherally, the fibroblastic component merges with ill defined trabeculae and sheets of unmineralized woven bone that harbour large osteocytes and demonstrate prominent osteoblastic rimming. In FP the bone is randomly distributed throughout the lesion. In some cases of MO, nodules of cellular hyaline cartilage with foci of enchondral ossification are present. Some late stage lesions of FP fuse with underlying periosteum and form an osteochondroma-like lesion. The most peripheral portions of MO are composed of well formed bony trabeculae and cortical-appearing bone which initially has a woven architecture but eventually is remodelled into lamellar bone. In most instances, the lesion is surrounded by a fibrous capsule that is typically oedematous in the early phases of development, but becomes progressively

more collagenous over time. This histological pattern of zonation is most evident in cases of MO that are of at least three weeks duration. Eventually, the central cellular areas become progressively quiescent such that over a period of years, the lush, richly cellular and proliferative fibroblastic centre is transformed into a paucicellular, collagenous zone that ultimately undergoes ossification. Some cases appear to regress completely. In the end, the residual ovoid mass is composed merely of cortical and cancellous bone with fatty or haematopoietic marrow. In some cases of MO, especially those occurring in more superficial soft tissues, the zonal pattern is not well developed and the reactive bone may be located throughout the lesion.

Immunophenotype

The immunohistochemical staining pattern reflects the bidirectional differentiation characteristic of MO and FP. The

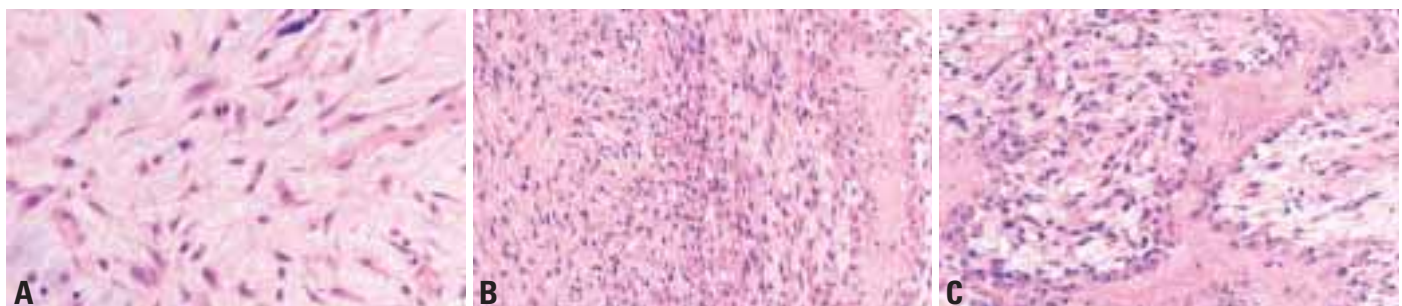


Fig. 2.09 Myositis ossificans. **A** Centre of MO composed of randomly arranged plump fibroblasts in a myxoid stroma. **B** Periphery of fibroblastic component merging with region containing trabeculae of woven bone. **C** Woven bone is prominently rimmed by osteoblasts.

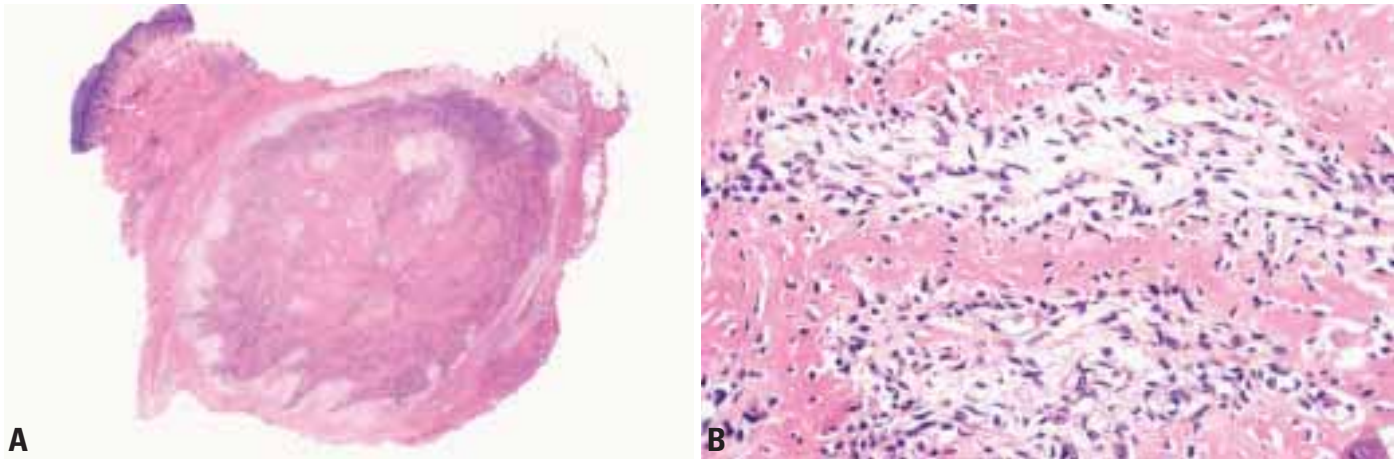


Fig. 2.10 **A** Fibroosseous pseudotumour of digits presenting as well circumscribed mass in subcutis. **B** Reactive woven bone lined by osteoblasts is present throughout the lesion.

centrally located fibroblasts and myofibroblasts express vimentin but may also stain with antibodies for actin, smooth muscle actin and desmin. The osteoblasts and osteocytes located in the periphery of the tumour typically express vimentin and osteocalcin.

Ultrastructure

The spindle cells have the characteristic ultrastructural features of fibroblasts and myofibroblasts including dilated rough

endoplasmic reticulum and aggregates of cytoplasmic filaments occasionally associated with dense bodies [2,1722]. The bone forming cells demonstrate evidence of osteoblastic differentiation and contain many mitochondria and abundant dilated rough endoplasmic reticulum.

Prognostic factors

MO and FP have an excellent prognosis and rarely recur; however, lesions removed marginally or incompletely in

the early stage of development have been known to regrow. There are rare examples of MO transforming into osteosarcoma but most of these reports are not well documented. Therefore, although the possibility of malignant transformation exists, this should be regarded as an extremely rare event and patients should be treated conservatively.

Ischaemic fasciitis

M. Michal

Definition

Ischaemic fasciitis (IF) is a distinctive pseudosarcomatous fibroblastic proliferation typically occurring over bony prominences, usually in immobilized patients.

Synonym

Atypical decubital fibroplasia.

Epidemiology

Ischaemic fasciitis most often occurs in immobilized patients as a result of prolonged pressure and impaired circulation [114,1498,1691].

Sites of involvement

IF is usually localized over bony prominences subjected to intermittent pressure (e.g. greater trochanter or shoulder), where it forms a poorly circumscribed, painless soft tissue mass usually less than 10 cm in diameter [1498]. It is located in the subcutis, sometimes extending into the muscle tissue and dermis.

Clinical features

Most of the patients are elderly, with a peak incidence between the seventh and ninth decades of life. Patients are usually chronically immobilized. Females

are affected slightly more commonly than males.

Histopathology

Histologically, IF is composed of multinodular zones of fibrinoid (coagulative) necrosis, fibrosis, myxoid changes involving adipose tissue and areas of vascular proliferation. Necrosis has a characteristic appearance consisting of central zone of liquefactive, fibrinoid necrosis having sharp uneven borders, staining deeply red to violet by H&E staining [233,2338]. Foci of necrosis are frequently surrounded by a fringe or palisade of reactive fibroblasts and capillaries.

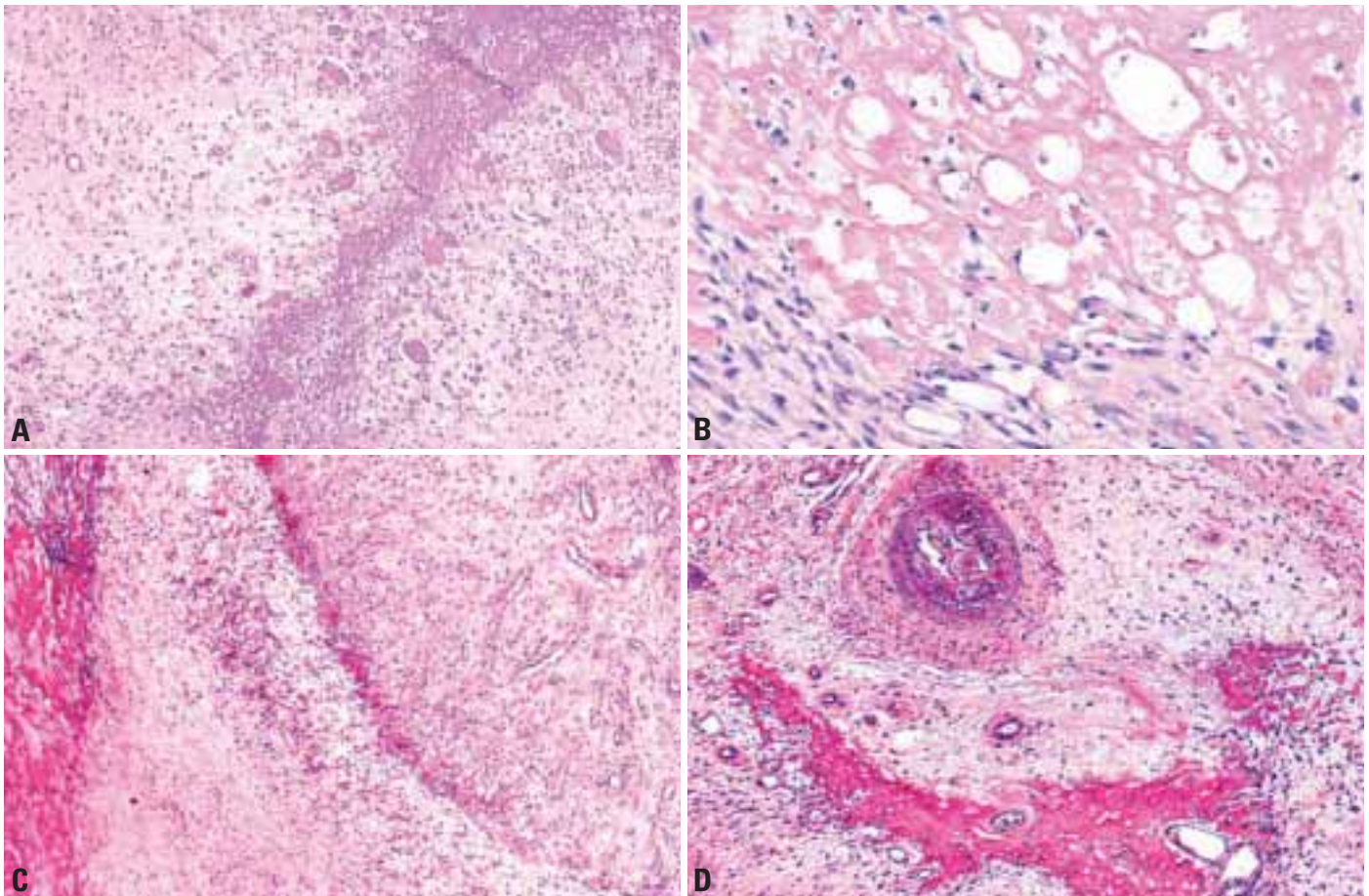


Fig. 2.11 Ischaemic fasciitis. **A** Medium power view showing fibrinoid necrosis and plump fibroblastic cells. **B** Note the prominent interstitial deposition of fibrin, associated with haemorrhage and reactive fibroblastic proliferation. **C** Foci of necrosis are frequently surrounded by a fringe or palisade of capillary proliferation and fibroblasts. **D** Necrosis has a characteristic appearance consisting of central zone of liquefactive and coagulative necrosis having sharp uneven borders, staining deeply red to violet by H&E. Muscular vessels reveal often a fibrinoid change within the wall with fibrin thrombi in various stage of recanalization.

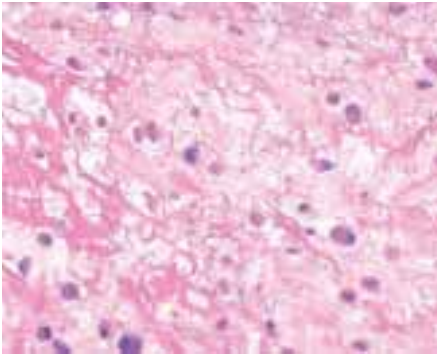


Fig. 2.12 Ischaemic fasciitis. High power view of the ganglion-like fibroblastic cells.

isade of capillary proliferation and fibroblasts. Muscular vessels reveal often fibrinoid change within the walls with fibrin thrombi in various stage of recanalization, and a small amount of secondary acute inflammation and extravasated RBC. Evidence of primary vasculitis or myositis is, however, never seen. Some of the fibroblasts are enlarged and even bizarre with abundant deep staining cytoplasm, large eccentric nuclei and smudged, hyperchromatic nucleus with prominent nucleoli. These cells resemble the fibroblasts in proliferative fasciitis.

Immunophenotype

Immunohistochemically the cells are vimentin positive and occasional fibroblastic cells are smooth muscle actin and CD68 positive. All cells are S100 protein and desmin negative. Enlarged, bizarre fibroblastic cells are CD34 positive {1498}.

Prognostic factors

These lesions may recur, due to persistence of the underlying cause rather than to intrinsic biological aggression. Most patients are cured by local excision.

Elastofibroma

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J.A. Bridge

Definition

An ill defined fibroelastic tumour-like lesion that occurs primarily in the soft tissue between the lower portion of the scapula and the chest wall of elderly persons and is characterized by a large number of coarse, enlarged elastic fibres.

ICD-O code 8820/0

Synonym

Elastofibroma dorsi.

Epidemiology

Although elastofibroma was originally considered as a rare lesion, there are geographically different distributions of this lesion, for example, many cases of elastofibroma have been detected in Okinawa, Japan {1526}. Elastofibroma or pre-elastofibroma-like changes have been found at autopsy in 13 to 17 % of elderly individuals {786,1030}.

Sites of involvement

Elastofibroma is almost always located in the connective tissue between the lower scapula and the chest wall, and lies deep to the latissimus dorsi and rhom-

boid major muscles, often with attachment to the periosteum of the ribs. Although it is unilateral in most cases, bilateral elastofibromas may be more common than previously recognized. Naylor et al. radiologically detected sub-clinical bilateral elastofibromas in many cases {1545}. Rare lesions have been reported in extrascapular locations, such as other parts of the chest wall, the upper arm, the hip region, and the gastrointestinal tract or other viscera.

Clinical features

Elastofibroma occurs almost exclusively in elderly individuals over the age of 50, with a peak between the seventh and eighth decades of life {1526}. There is a striking predominance in women. Elastofibroma is a slowly growing mass that only rarely causes pain or tenderness. Computed tomography (CT) and magnetic resonance imaging (MRI) allow a presumptive diagnosis of elastofibroma {1170}.

Aetiology

Although some have suggested that elastofibroma may be a response to repeated trauma or friction between the

lower scapula and the underlying chest wall {1031}, this has never been confirmed, particularly for examples located in extrascapular sites. Nagamine et al. described that approximately one-third of 170 patients with this lesion in Okinawa occurred within the same family lines, supporting a genetic predisposition in at least some patients {1526}. Enjoji et al. reported an elastofibromatous lesion of the stomach at the base of a peptic ulcer in a patient with bilateral subscapular elastofibromas, suggesting the possibility of an underlying systemic enzymatic defect {585}. The accumulation of large irregular elastic fibres in this lesion may be the result of abnormal elastogenesis rather than degeneration of preexisting elastic fibers.

Macroscopy

Elastofibroma is usually ill defined and rubbery, and exhibits grey-white fibrous tissue with interposing small areas of yellow fat. The mass varies from 2 cm up to 15 cm in diameter.

Histopathology

The lesion is composed of a mixture of paucicellular collagenous tissue and

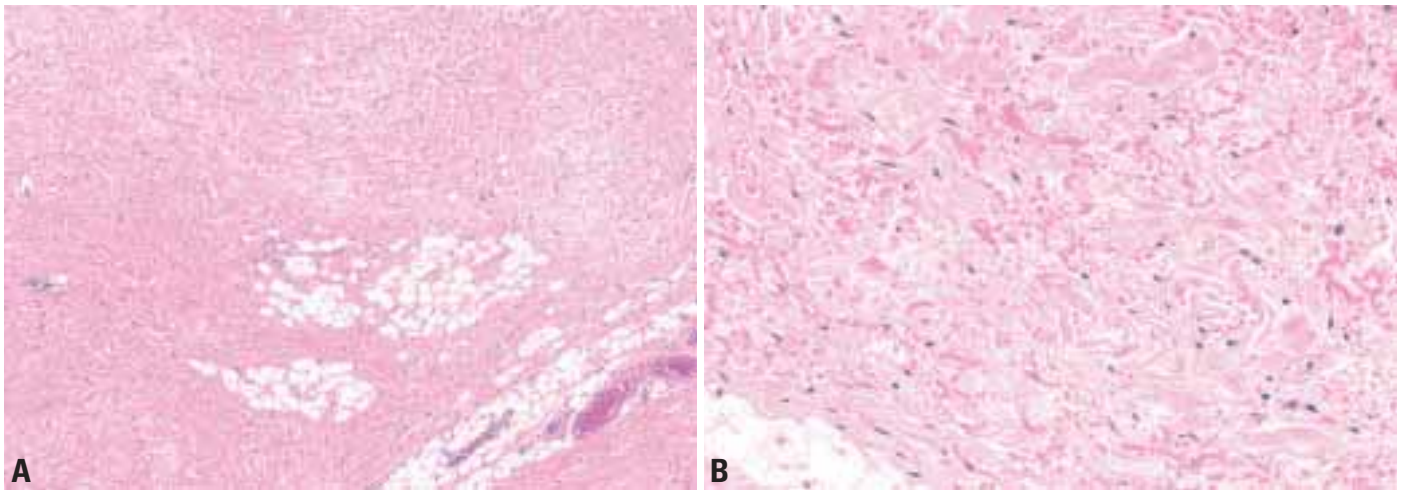


Fig. 2.13 Elastofibroma. **A** Paucicellular collagenous tissue and entrapped mature fat cells. **B** Large, coarse, densely eosinophilic elastic fibres admixed with collagen in an elastofibroma.

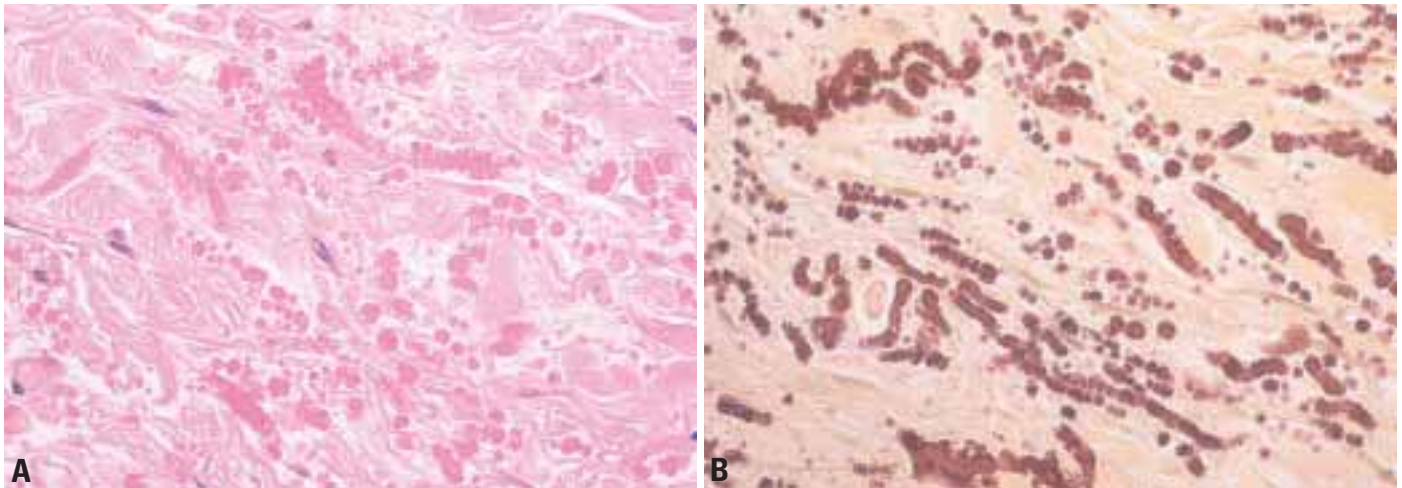


Fig. 2.14 Elastofibroma. **A** Elastic fibres arranged like beads or globules with serrated edges on a string in an elastofibroma. **B** Weigert's elastic stain highlights the bead-like arrangement of the abnormal elastic fibres in an elastofibroma.

large numbers of elastic fibers, associated with small amounts of mucoid stroma and entrapped mature fat cells. The elastic fibres are large, coarse, deeply eosinophilic, and fragmented into small, linearly arranged globules or serrated disks simulating beads on a string. Elastic stains reveal the large branched or unbranched fibres to have a dense core and irregular serrated margins. Although the elastin-like material is removed by prior treatment of the sections with pancreatic elastase, it is more resistant to the digestion than that of control skin {1531}.

Immunohistochemistry

The elastic fibres in elastofibroma are reactive with a specific antibody to elastin {733,1182}.

Ultrastructure

Elongated or globular masses with a central core of more electron-lucent material like mature elastic tissue surrounded by a fibrillary electron-dense substance like immature elastin are seen in a collageous stroma {159,733,1118,1182,1753}. The constituent cells in close proximity to the elastic fibres have ultrastructural features of fibroblasts and myofibroblasts, some of which contain non-membrane-bounded dense granular bodies with an intensity similar to that of extracellular elastin in the cytoplasm, suggesting that these cells produce the extracellular elastin.

Genetics

Cytogenetic investigations of elastofibroma reveal that this lesion exhibits signifi-

cant chromosomal instability manifested as both clonal and non-clonal structural changes {141,1370,2188}. Aberrations of the short arm of chromosome 1 are particularly prominent. Additional studies are needed to define the potential biological significance of these chromosomal abnormalities in elastofibroma. The observation of familial occurrences of elastofibroma supports a genetic predisposition to this lesion of controversial aetiology {1526,1884}.

Prognostic factors

Elastofibroma is cured by simple excision. Local recurrence is very rare.

Fibrous hamartoma of infancy

H. Hashimoto

Definition

A paediatric, benign, poorly circumscribed, superficial soft tissue mass characterized by an organoid mixture of three components: well defined intersecting trabeculae of dense fibrocollagenous tissue, loosely textured areas of immature-appearing, small, rounded, primitive mesenchymal cells, and mature fat.

Epidemiology

Although in overall terms fibrous hamartoma of infancy is rare, accounting for approximately 0.02 % of all benign soft tissue tumours [1016], this lesion is one of the relatively more common tumours of fibrous tissue in early childhood.

Sites of involvement

Fibrous hamartoma of infancy occurs most frequently in the anterior or posteri-

or axillary fold, followed by the upper arm and shoulder, thigh, groin, back, and forearm [590,1476,1638,1998]. This lesion arises only exceptionally in the hands and feet [1029,1034,1794]. The feature helps distinguish fibrous hamartoma of infancy from calcifying aponeurotic fibroma, which occurs almost exclusively in the hands or feet.

Clinical features

The majority of fibrous hamartomas of infancy present in the first 2 years of life and up to 25 % are discovered at birth [519,570,590,1638]. They do not occur after puberty, although rare lesions have been reported in older infants. There is a striking predominance in boys [1638,1998], but there is no evidence of familial tendency or of association with any other congenital disorder. Fibrous hamartoma of infancy is almost always a

solitary lesion, and usually a rapidly growing, freely movable mass in the subcutis or dermis, occasionally being attached to the underlying fascia and only rarely involving the skeletal muscle.

Macroscopy

Fibrous hamartoma of infancy is usually poorly circumscribed and exhibits grey-white tissue alternating with yellow fat. The amount of the fatty component varies from case to case. Most lesions are less than 5 cm in diameter, but tumours rarely reach larger than 10 cm [519].

Histopathology

Fibrous hamartoma of infancy is characterized by three distinct components forming organoid structures. The well defined intersecting trabeculae of dense fibrocollagenous tissue are composed of fibroblastic and myofibroblastic spindle cells with bland, straight or wavy nuclei separated by varying amounts of collagen. The loosely textured islands interspersed among the fibrous trabeculae are made up of immature-appearing, small, rounded or stellate, primitive mesenchymal cells with scant cytoplasm embedded in a myxoid matrix containing abundant hyaluronidase-sensitive acid mucopolysaccharides. The primitive myxoid areas are frequently oriented around small veins. Mitotic figures are absent or few in either the fibroblastic or myxoid areas. The mature fat component is interspersed among the other two components. The relative proportions of these three components vary considerably between cases. Fat may be recognized only at the periphery or may be the major component. In some cases, especially in older children, a pronounced sclerosing process, that is somewhat reminiscent of disorderly fibrosis or neurofibroma, replaces the majority of the lesion [590].

Immunohistochemistry

Both the fibroblastic and primitive cells are positive for vimentin. There are

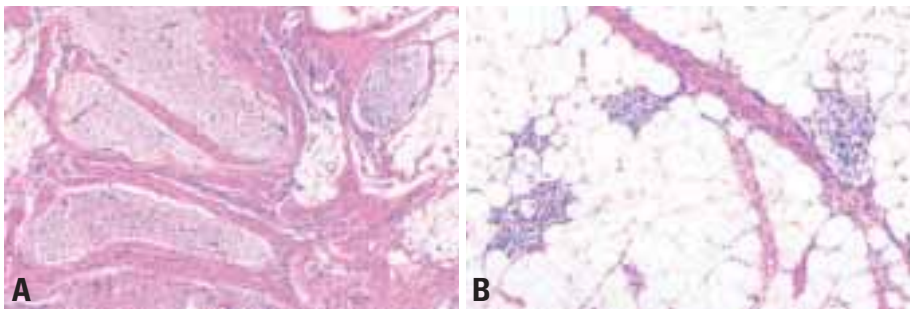


Fig. 2.15 Fibrous hamartoma of infancy. **A** Organoid pattern composed of trabeculae of dense fibrocollagenous tissue, with typical islands of loosely arranged spindle cells, and mature fat cells. **B** This case shows three distinct components, with mature fat predominating.

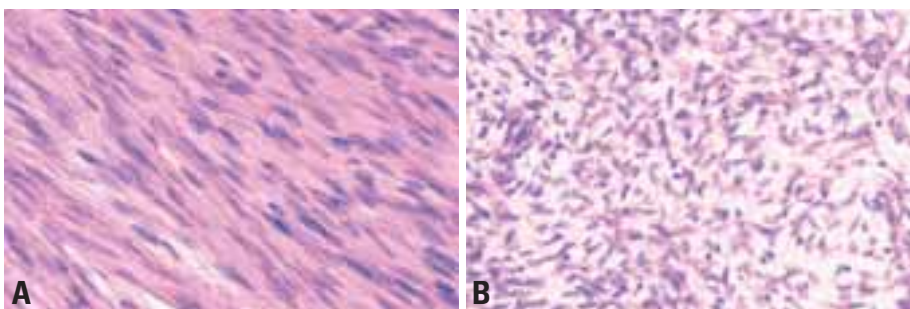


Fig. 2.16 Fibrous hamartoma of infancy. **A** Spindle cells in fibrous trabeculae are composed of bland fibroblastic or myofibroblastic cells with straight or wavy nuclei. **B** In the myxoid islands, note bland primitive spindle cells with scant cytoplasm.

actin-positive spindle cells only in the trabeculae, probably indicating myofibroblastic differentiation {686,845,1440}. Desmin is usually negative, although some have described positive immunoreactivity to desmin in the trabecular component {845}.

Ultrastructure

A mixture of fibroblastic and myofibroblastic cells are seen in the trabecular component {830,845,1440}, whereas primitive mesenchymal cells with slender cytoplasmic processes and few intracytoplasmic organelles are found in the loosely textured myxoid areas.

Prognostic factors

Fibrous hamartoma of infancy is benign and usually cured by local excision. Rare recurrences are cured by reexcision {519,590,1998}.

Myofibroma / Myofibromatosis

B.P. Rubin
J.A. Bridge

Definition

Myofibroma and myofibromatosis are terms used to denote the solitary (myofibroma) or multicentric (myofibromatosis) occurrence of benign neoplasms composed of contractile myoid cells arranged around thin-walled blood vessels. Myofibroma(tosis) forms a morphological continuum with myopericytoma and so-called infantile haemangiopericytoma.

ICD-O codes

Myofibroma 8824/0
Myofibromatosis 8824/0

Synonyms

Infantile myofibromatosis, congenital generalized fibromatosis.

Epidemiology

Solitary and multicentric lesions can occur over an extremely wide age range that extends from newborns to the elderly {151,353,431,1970}. However, many cases are detected at birth or within the first two years of life. Myofibroma(tosis) is more common in males {353}. There are rare familial cases (see discussion of genetics). The relative frequency of solitary versus multicentric forms is unclear from the literature {353,2284}. This may be due to methodological differences in the types and completeness of radiological studies that were performed, as many lesions, even deep lesions and

those affecting bone, may not be clinically apparent. In adults, solitary lesions are more common than multicentric tumours and this is probably also the case in children.

Sites of involvement

Approximately half of solitary myofibromas occur in the cutaneous/subcutaneous tissues of the head and neck region, followed by trunk, lower, and upper extremities {353}. The other half occur in skeletal muscle or aponeuroses, with a small number involving bone, predominantly the skull {353,894,1007,1111}. Myofibromatosis (i.e., multicentric disease) involves both soft tissue and bone and frequently (from 15-20% of the time) occurs in the deep soft tissues and at visceral locations, including the lungs, heart, gastrointestinal tract, liver, kidney, pancreas, and rarely, the central nervous system {17,48,1828,1846}. Any bone can be involved but most often, the long bones are affected.

Clinical features

Lesions can be of short or of longstanding duration {431,679}. Cutaneous lesions have the appearance of purplish macules, simulating a vascular neoplasm. Subcutaneous lesions occur most often as painless, freely mobile masses while more deeply seated lesions may be fixed. Visceral lesions may cause symptoms referable to the

organs that are involved. The radiological appearance of soft tissue lesions varies greatly, and can be well-circumscribed or infiltrative, often with calcification, either within or surrounding the lesions. Bony lesions characteristically occur as multiple elongated radiolucent lesions within the metaphyseal regions, sparing the region immediately adjacent to the epiphysis {1992}. A sclerotic margin forms invariably in more mature lesions, which also have central mineralization.

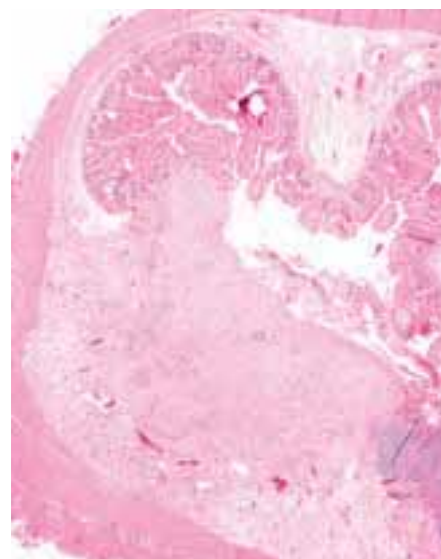


Fig. 2.17 580 Myofibroma / Myofibromatosis. Small bowel lesion in a newborn.

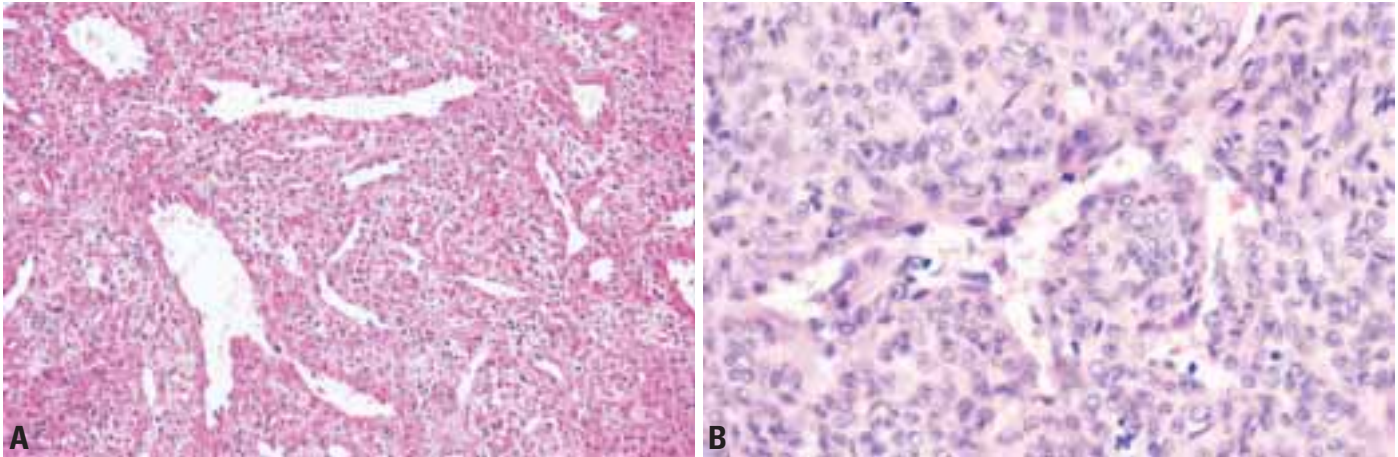


Fig. 2.18 Myofibroma / Myofibromatosis. **A** Primitive spindle cells with haemangiopericytoma-like blood vessels. **B** Note the perivascular growth pattern, underlying the close relationship with myopericytoma.

Aetiology

The aetiology of myofibroma(tosis) is unclear. There are rare familial cases, indicating a genetic component (see discussion of genetics).

Macroscopy

Nodules vary greatly in size, from 0.5 to 7 cm, with a median size of 2.5 cm {353}. Lesions within the dermis and subcutaneous tissue are better defined than those in the deep soft tissues and viscera. On cut surface, myofibromas have a firm, fibrous cut surface and are greyish white, light tan to brown, or purplish in colour. They often have central yellow / necrotic areas and / or cystic spaces filled with caseous-like material or haemorrhage.

Histopathology

At low power, there is a nodular or multinodular proliferation with a zoned appearance, due to regional variation of cell types. Usually within the periphery of the nodules, there are plump myofibroblasts arranged in short fascicles or whorls. These myofibroblasts are spindle shaped with pale pink cytoplasm and have elongated, tapering nuclei with a vesicular chromatin pattern and one or two small nucleoli. There is no significant atypia or pleomorphism. These myoid whorls or nodules often hyalinize, with a pseudochondroid appearance. Within the centre of the nodules, are less well differentiated, rounded, polygonal, or spindle-shaped cells, with slightly larger, hyperchromatic nuclei. These cells have relatively scant cytoplasm, and are arranged around thin-walled, irregularly

branching, haemangiopericytoma-like blood vessels {2037}. Occasional cases have a more random distribution of the two cell types and in some cases, the arrangement can be completely reversed (haemangiopericytoma-like appearance at the periphery and myofibroblastic cells in the middle) {151,353}. The haemangiopericytomatous component can predominate and this has led to the suggestion that most cases of so-

called infantile haemangiopericytoma, are actually cases of myofibroma(tosis) {353,1412}. Calcification, necrosis and stromal hyalinization are identified frequently. Mitotic activity is usually minimal although exceptional cases can have up to 10 per 10 high power fields. Another histological feature which merits attention, is the frequent presence of intravascular growth, which can lead to the mistaken diagnosis of malignancy {151,

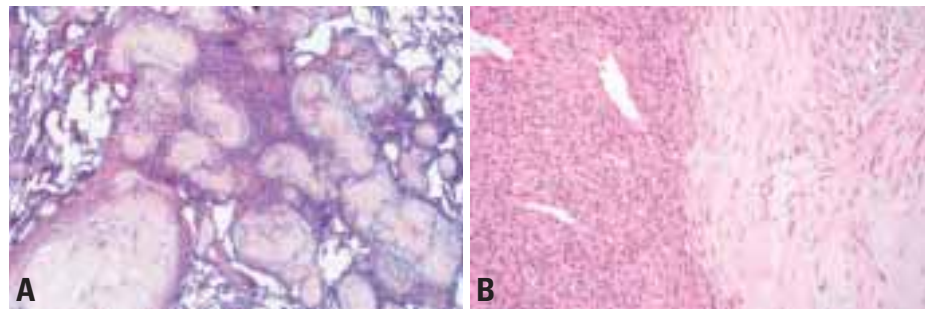


Fig. 2.19 Infantile myofibromatosis. **A** Lung is one of the more common visceral locations to be affected. Note the typically multinodular growth pattern. **B** High power view showing the typical cytologic features. On the left are the rounded, less well differentiated cells arranged around haemangiopericytoma-like blood vessels and on the right are the spindle-shaped myoid cells.

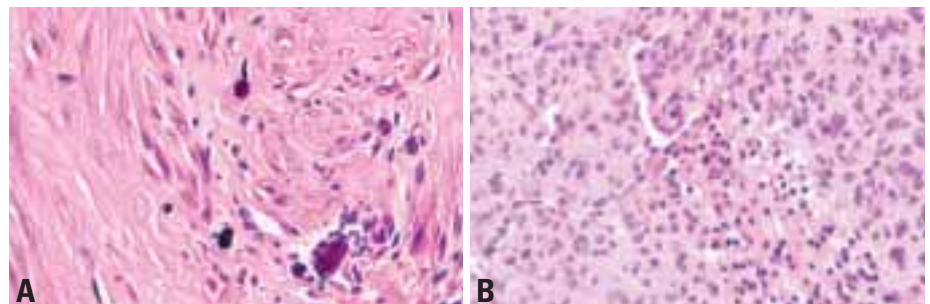


Fig. 2.20 Myofibroma / Myofibromatosis. **A** Focal calcification in a myoid area. **B** Both necrosis and apoptosis are often identified.

353}. This intravascular growth is in fact subendothelial and is not associated with true metastatic potential.

Immunophenotype

Both the myofibroblastic and more primitive component are positive for vimentin and smooth muscle actin, while the myofibroblastic component is more strongly positive for pan-actin HHF-35. Both components are negative for S100 protein, epithelial membrane antigen, and keratin {431,1412}.

Ultrastructure

Typical are prominent dilated rough endoplasmic reticulum, longitudinal filament bundles with dense bodies, and focal basal lamina {151,161,224,523,894}.

Genetics

Familial occurrence is too rare to allow any firm conclusions regarding the genetics of myofibromatosis. However, the documentation of affected cousins, half-siblings, and parent-offspring pairs suggests an autosomal dominant inheritance pattern {244,1037,2070}. The true incidence of myofibromatosis occurring in a familial setting may be higher than it appears as the lesions are frequently small and asymptomatic and tend to disappear spontaneously and thus, milder expressions of the disease in relatives could easily be overlooked {244}.

Prognostic factors

Some myofibromas regress spontaneously {146,161,353}. A small number

of solitary lesions (<10%) recur, but there do not appear to be any factors that are predictive of recurrence and these recurrences are cured by local re-excision {353}. The extent and location of the visceral lesions determines the prognosis, with involvement of vital organs, leading to cardiopulmonary or gastrointestinal complications, causing death in rare cases {40,353,2284}. Pulmonary involvement appears to be an especially bad prognostic factor.

Fibromatosis colli

J. O'Connell

Definition

A benign, site-specific lesion that occurs in the distal sternocleidomastoid muscle of infants. The mass results in fusiform thickening of the muscle and cervico-facial asymmetry due to its shortening (torticollis).

Synonyms

Congenital muscular torticollis, sternocleidomastoid tumour of infancy, pseudotumour of infancy.

Epidemiology

Fibromatosis colli is uncommon. It occurs in approximately 0.4% of live births {1187}. There is no sex predilection. The majority of affected infants are diagnosed before 6 months of age {1187}. There is a high incidence of abnormal intrauterine positioning or difficult delivery in the affected infants {198,

1187,1863}. Additionally, there is a clear association with other musculoskeletal developmental abnormalities that are associated with abnormal intrauterine positioning, including forefoot anomalies and congenital hip dislocation {198,1187,1863}.

Site of involvement

Fibromatosis colli typically affects the lower one-third of the sternocleidomastoid muscle. There is no predilection as to side.

Clinical features

The affected infants present with a smooth fusiform swelling of the distal sternocleidomastoid muscle {198,1187,1863}. This usually measures less than 5.0 cm in length. The muscle typically is expanded although it rarely measures greater than 2.0 cm in width. Typically

the infants exhibit cervico-facial asymmetry with facial tilt due to the shortening



Fig. 2.21 Fibromatosis colli. Plain X-ray showing a soft tissue mass in the region of sternocleidomastoid muscle.

of the affected muscle {198,1187,1228, 1863}. Ultrasound investigation is useful and non-invasive. It demonstrates a uniform isoechoic mass confined to the muscle {407}. In real time this can be shown to move with the action of the muscle.

Aetiology

It is most likely that fibromatosis colli represents a cellular scar-like reaction to injury of the sternocleidomastoid muscle acquired in the last trimester of intrauterine growth, or at the time of delivery {198, 1187,1863}.

Macroscopy

The lesion appears as a tan gritty mass confined to the muscle. Regions of haemorrhage or necrosis are not present.

Histopathology

Like many presumed reactive proliferations, the microscopic appearance of fibromatosis colli varies depending on the time at which it is examined. Currently the favoured investigation of these masses is by fine needle aspiration cytology {1187}. This demonstrates cellular specimens with aggregates of uniform plump spindle cells embedded in myxoid to collagenous ground substance {1187}. Multinucleated skeletal myocytes may be admixed. These aspiration specimens correspond to the cellular proliferative phase of the process. Surgical specimens, which are obtained only from a minority of the patients at the time of tenotomy for persistent torticollis, usually demonstrate less cellular collagen-rich tissue that resembles scar or conventional fibromatosis. In these the lesion is composed of uniform plump fibroblastic and myofibroblastic cells embedded in a collagenous background {198,1228,1863}. Infiltration and entrapment of skeletal myocytes is evident.

Immunophenotype

The lesional cells exhibit positive staining for vimentin and muscle actins.

Prognostic factors

When diagnosed early, fibromatosis colli is managed in a non-surgical manner.

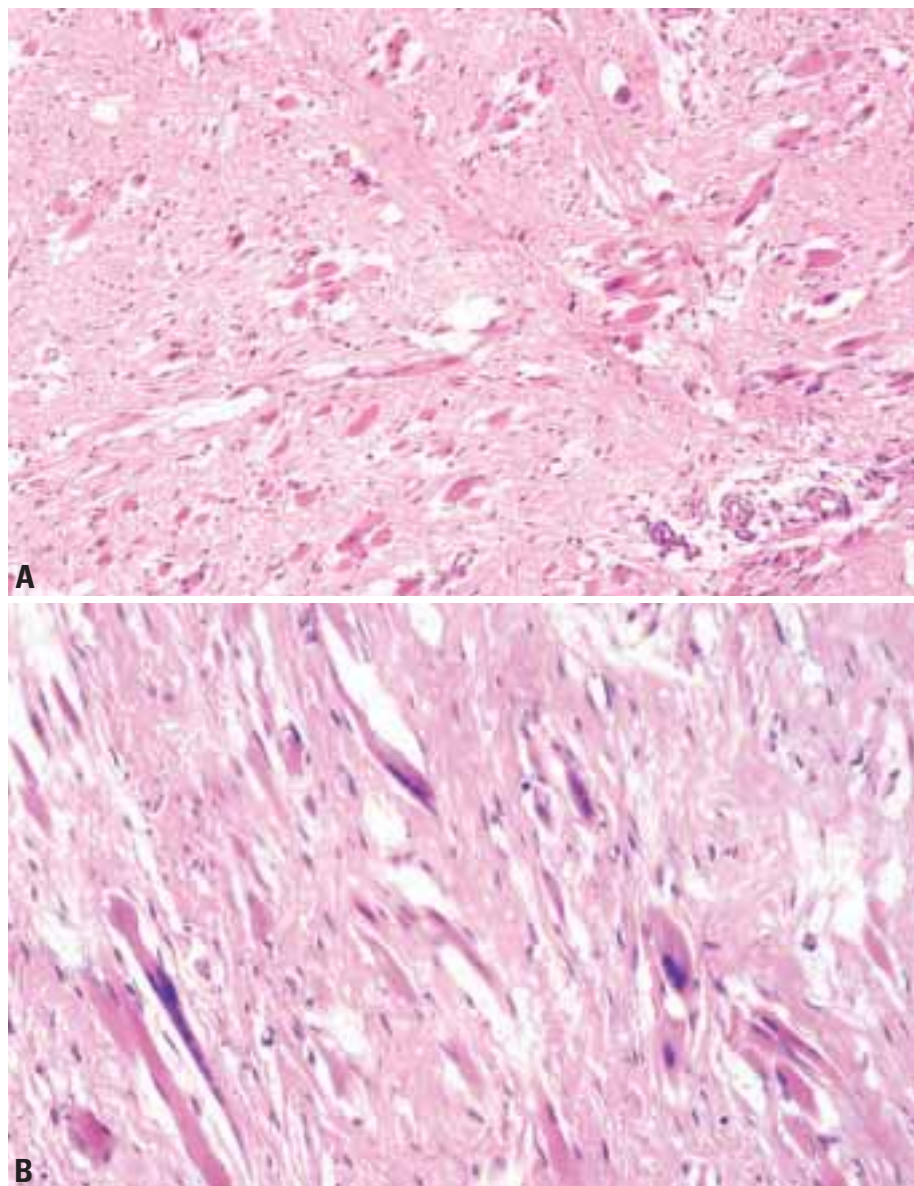


Fig. 2.22 Fibromatosis colli. **A** Note the diffuse pattern of scar-like fibroblastic proliferation within sternocleidomastoid muscle. **B** The entrapped skeletal muscle fibres commonly show both degenerative and reactive sarcolemmal nuclei.

The treatment involves passive stretching and physiotherapy {198}. Seventy percent of children will have complete resolution of the mass and demonstrate normal cervico-facial posture and movement with this approach {198}. Surgical intervention, principally tenotomy, is required in between 10 to 15% of patients {198}. Overall, 90% of patients achieve normal function and appearance

following timely intervention {198}. The prognosis is worse in those infants who are diagnosed and treated when older than 1 year.

Juvenile hyaline fibromatosis

J. O'Connell

Definition

An apparently non-neoplastic disorder that typically presents in infancy, characterized by the accumulation of extracellular "hyaline material" within skin, somatic soft tissues and the skeleton, resulting in tumour-like masses. The hyaline material is produced by an aberrant population of fibroblasts. The clinical manifestations vary depending on the number, location and growth rate of the masses.

Synonyms

Molluscum fibrosum, mesenchymal dysplasia.

Epidemiology

Juvenile hyaline fibromatosis is an extremely rare disorder {1057,1094,1313}. As of 1998 less than 50 cases had been reported in the literature {2279}. It typically presents in infancy {1057,1094,1313,2279}. There is no sex predilection and affected infants are often the progeny of consanguineous parents {1057,1094,1313,2279}. The clinical phenotype of affected children varies {1313}. Most of the time there is progressive increase in the number and size of superficial and deep nodules with resulting deformity and dysfunction. Survival into adulthood may occur {1078,1094}.

Sites of involvement

The tumour-like masses of hyaline material develop in the skin (particularly the face and neck resulting in papules and nodules), gums (producing "gingival hyperplasia"), periarticular soft tissues (resulting in joint contractures) and bones (especially the skull, long bones and phalanges) {1057,1078,1094,1313,2279}.

Clinical features

Patients present with skin papules affecting the face and neck, in particular, around the ears. Perianal skin papules may resemble genital warts. Periarticular deposits of the hyaline material result in joint contractures, particularly involving the knees and elbows {1057,1078,1094,

1313,2279}. Imaging studies reveal generalized osteoporosis and discrete lytic lesions in the affected bones {1057,1094,1480}.

Aetiology

The aetiology of juvenile hyaline fibromatosis is unknown. It appears to be transmitted in an autosomal recessive manner {1057,1094,1313}. Biochemical investigation of the hyaline material suggests increased extracellular chondroitin sulphate, and types I and VI collagen {250,1073}. Recently it has been suggested the fundamental defect may be a reduction in type III collagen production {250}.

Macroscopy

The nodules have a uniformly solid, white or waxy appearance.

Histopathology

The individual nodules obliterate the normal tissues in which they are found. They are composed of an admixture of plump fibroblastic cells associated with extracellular uniform hyaline material that is non-fibrillar and eosinophilic in haematoxylin and eosin stains. In younger patients or "newer lesions" the nodules are relatively more cellular {1362,1480}. The constituent fibroblasts have clear cytoplasm and may exhibit a vague fascicular arrangement. Nuclear atypia or necrosis is not seen. Older lesions are less cellular and the fibroblasts may appear compressed by the extracellular material. PAS stain is strongly positive and diastase resistant.

Immunophenotype

The fibroblastic cells label positively for vimentin. Stains for muscle actin and S100 protein are negative {14,1920}.

Ultrastructure

The lesional cells are fibroblasts and demonstrate numerous cystically dilated membrane-bound vesicles. These contain granular and filamentous material similar to the extracellular ground sub-

stance. Continuity between the vesicles and the extracellular space may be evident {1057,1313,1480,2279}.

Prognostic factors

The lesions are treated by surgical excision depending on their location. Local recurrence rates are high {1057}. The



Fig. 2.23 Juvenile hyaline fibromatosis. Multiple subcutaneous nodules on the scalp and face are the most consistent finding.

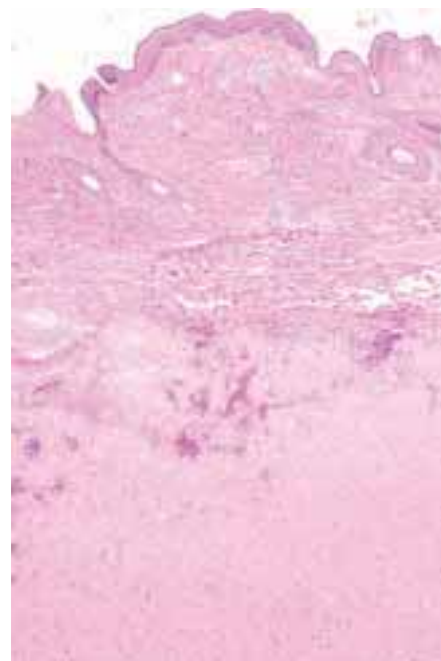


Fig. 2.24 Juvenile hyaline fibromatosis. Low power view of a typically well circumscribed hypocellular nodule in deep dermis / subcutis.

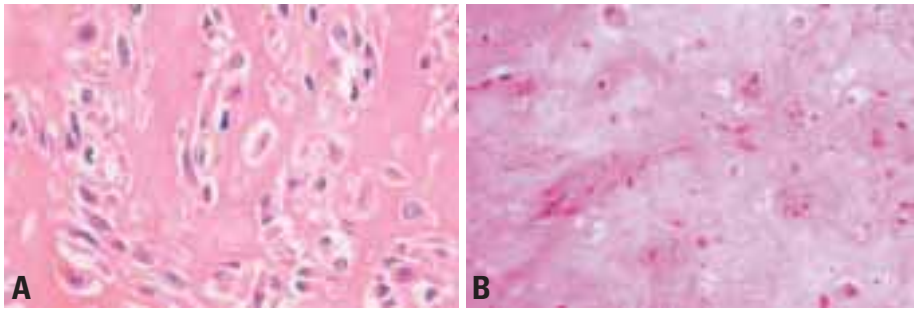


Fig. 2.25 Juvenile hyaline fibromatosis. **A** Cellular focus of a nodule. Note the clustered arrangement of the fibroblasts and the extracellular amorphous material. **B** An older nodule that is less cellular and dominated by the hyaline material.

prognosis is determined by the number, size and location of the nodules and the degree of the patient's functional impairment. A single case of oral squamous carcinoma arising in association with juvenile hyaline fibromatosis has been reported {1078}.

Inclusion body fibromatosis

J. O'Connell

Definition

A benign proliferation of fibroblastic and myofibroblastic cells that typically occurs on the digits of young children. It is named for the intracytoplasmic inclusions that are detected in a minority of the lesional cells.

Synonyms

Infantile digital fibromatosis, digital fibrous tumour of childhood, infantile digital fibroma.

Epidemiology

Inclusion body fibromatosis is rare.

Site of involvement

Typically, lesions develop on the dorsal aspect of digits of the hands or feet {148, 344,913,1791}. In a minority, more than one digit may be affected synchronously or asynchronously. Involvement of the thumb or big toe is extremely unusual. Rarely inclusion body fibromatosis occurs in extra-digital sites such as the soft tissues of the arm and breast {1702, 1738}.

Clinical features

Patients typically present in the first year of life {148,344,913,1791}. There is no

sex predilection. Occasionally clinically typical lesions present in older patients and conversely pathologically characteristic tumours occasionally develop in sites other than the digits {1702,1738}. Treatment is by local excision, with an effort to preserve function. Digital examples present as dome shaped swellings overlying the phalanges or interphalangeal joints. The nodules usually measure less than 2.0 cm and the overlying skin is typically taught and stretched. Occasional examples may erode bone. The extra-digital nodules present as non-specific soft tissue masses.



Fig. 2.26 Inclusion body fibromatosis. Two phalangeal nodules overlying the distal interphalangeal joints. Note the stretched overlying skin.

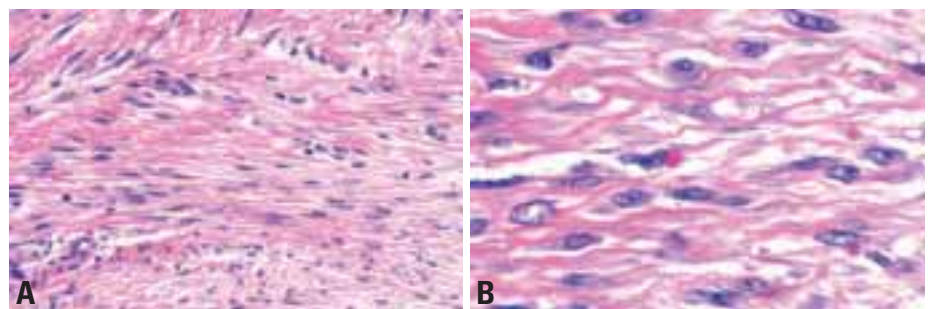


Fig. 2.27 Inclusion body fibromatosis. **A** Low power view demonstrating intersecting fascicles of spindle cells associated with extracellular collagen. **B** High power view shows the plump spindle cells, uniform nuclei and scattered intracytoplasmic eosinophilic round inclusions.

Macrosocopy

The lesions have a uniform white / tan appearance. They lack regions of haemorrhage or necrosis. They are typically ill defined.

Histopathology

The nodules are composed of intradermal sheets and fascicles of uniform spindle cells associated with varying amounts of extracellular collagen {344, 913,1702,1738}. They are non-encapsulated and fascicles of cells extend into adjacent tissues. Individual cells have central elongated nuclei and vaguely fibrillar cytoplasm. The diagnostic feature is the presence of intracytoplasmic, eosinophilic spherical "inclusions" {344, 913,1702,1738}. Inclusions are brightly trichrome positive and PAS negative. These are present in a minority of the cells and are not always uniformly distributed. The lesional cells lack nuclear atypia and mitoses are not prominent.

Immunophenotype

The lesional cells demonstrate positive staining for vimentin, and muscle actins {344,1515,1516,1702}. The latter stains often exhibit a parallel linear pattern beneath the cell membrane, in a so-called "tram-track" pattern. The eosinophilic globules demonstrate variable staining for actins in formalin fixed material {1515,1516,1702}. These vari-

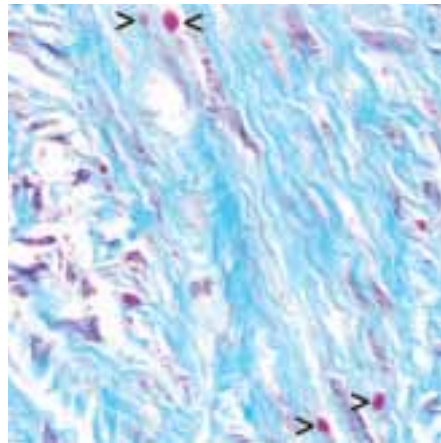


Fig. 2.28 Inclusion body fibromatosis. Masson trichrome stain shows the typical purple-red juxtannuclear rounded inclusions.

able results appear to be dependent upon the method of tissue preparation prior to immunohistochemical staining. Pretreatment with KOH has been reported to aid in demonstrating a positive staining result for actins within the inclusions {1515}.

Ultrastructure

The lesional spindle cells demonstrate ultrastructural features of myofibroblasts {344,913,1020,1516,1702}. They exhibit well formed rough endoplasmic reticulum and intracytoplasmic aggregates of filaments. These are concentrated

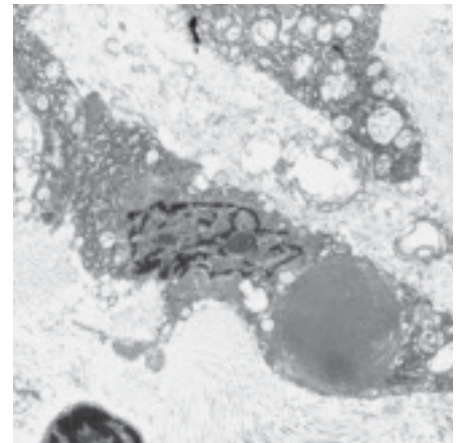


Fig. 2.29 Inclusion body fibromatosis. Myofibroblastic cell with a typical intracytoplasmic granular filamentous inclusion.

beneath the cell membrane and focally show dense bodies. The inclusions lie free in the cytoplasm and have a granular / filamentous appearance {344,913, 1020,1516,1702}. Cytoplasmic actin filaments extend into the granular inclusions and may be demonstrated to be continuous with them {913}.

Prognostic factors

Local recurrence occurs in about 50% of cases {148,1791}. The main prognostic indicator is the adequacy of the primary excision. Metastasis does not occur.

Fibroma of tendon sheath

G. Farshid
J.A. Bridge

Definition

Fibroma of tendon sheath (FTS) is an uncommon, small, benign fibrous nodule that arises near tendinous structures, mostly in the hands of adult males.

ICD-O code 8810/0

Synonym

Tenosynovial fibroma.

Epidemiology

Most patients are in the fourth decade but FTS can occur at any age. Approximately 60% of lesions affect males. In the hands the right side is favoured. Multiplicity of lesions is rare. Familial or racial clustering is not reported.

Site of involvement

The thumb, index and middle fingers are the favoured sites of origin. Together with lesions of the volar aspect of hand and wrist, they account for 80% of cases. The anterior knee and plantar aspect of the foot are less commonly involved. Arms, elbows, toes, temporomandibular joint, trunk and neck are rarely affected.

Clinical features

FTS typically presents as a small, firm, slowly enlarging, painless mass. Impingement on nerves, carpal tunnel syndrome, pain, finger triggering and ulceration may occur.

A heterogeneous and lobulated mass with low signal intensity both in T1- and T2-weighted images may be seen on MRI. Smooth erosion into bone has been reported {2002}.

Aetiology

The predilection for specific digits of the right hand and the finding of fasciitis-like areas in some cases suggest a possible reactive origin. Injury is reported in 10% of cases. Clonal chromosome abnormalities have been demonstrated in one case.

Macroscopy

FTS forms a sharply-demarcated, multi-lobated and sometimes multinodular, fibrous mass, almost always <3 cm in diameter. The cut surface is homogeneous, pale and solid.

Histopathology

FTS is composed of well-circumscribed nodules separated by deep, narrow clefts. The nodules are typically paucicellular, containing spindled fibroblasts embedded in a collagenous stroma. Scattered slit-like vascular channels are frequent {103,352,905,981,1736}. Some lesions may show hypercellularity, but the cellular areas usually merge with more typical paucicellular zones. These hypercellular examples resemble nodular fasciitis and often display typical mitotic figures, but coagulative necrosis

and nuclear hyperchromasia are not seen. Other less common histological features may include presence of stellate cells, pleomorphic bizarre cells, myxoid change, cyst formation, dense hyalinization and chondroid or osseous metaplasia.

Immunophenotype

The cells of FTS express SMA and vimentin.

Ultrastructure

Features of fibroblasts and myofibroblasts are identified.

Genetics

A clonal chromosomal abnormality, t(2;11)(q31-32;q12), has been described in one case {440}. Notably, an identical translocation has also been observed in desmoplastic fibroblastoma {1911}.

Prognostic factors

Up to 24% of lesions in the hands recur months to years after the diagnosis, sometimes repeatedly but non-destructively {352}. Because of adherence to tendinous structures local excision may be difficult. In view of their non-aggressive course, excision should aim to relieve symptoms but preserve function. Metastasis has never been reported in FTS.

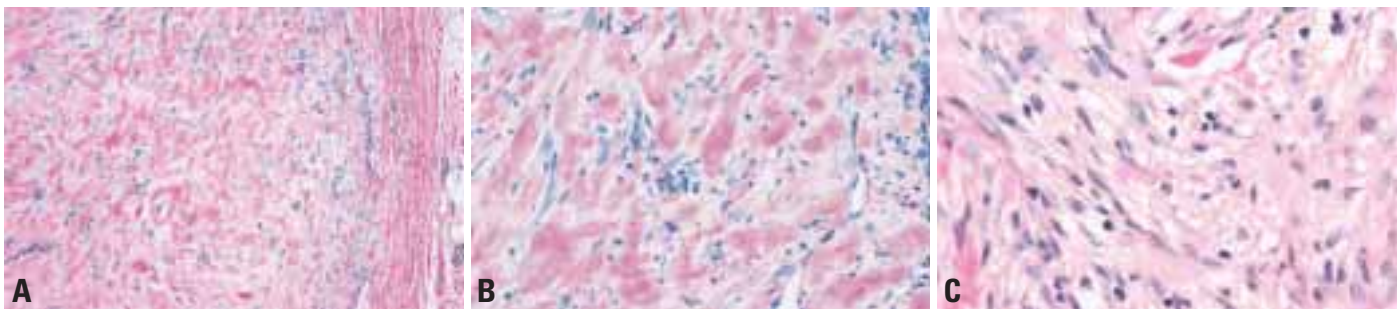


Fig. 2.30 Fibroma of tendon sheath. **A** Border of a well circumscribed nodule, showing **(B)** paucicellular spindle fibroblasts in a collagenous stroma. **C** Detail of a more cellular lesion.

Desmoplastic fibroblastoma

M.M. Miettinen
J.A. Bridge

Definition

A rare, benign, paucicellular tumour affecting mainly adult males, characterized by densely collagenous, predominantly stellate-shaped fibroblasts exhibiting bland cytological features. Myxoid stroma may be present.

ICD-O code 8810/0

Synonym

Collagenous fibroma.

Clinical features

This relatively uncommon tumour is usually diagnosed in men between the 5th and 7th decades (70%), and rarely in adolescents; only 25% of cases have been diagnosed in women. The tumour typically presents as an asymptomatic mass involving the subcutis, but fascial involvement is common and up to 25% of

cases involve skeletal muscle. It occurs in a variety of peripheral sites with the most common locations being the arm, shoulder, lower limb, back, forearm, hands and feet. The behaviour is benign, and none of the published clinicopathologic series had recurrences {622,900, 1447,1560}.

Macroscopy

The tumour is usually relatively small, measuring 1-4 cm in greatest dimension, but examples over 10 cm and as large as 20 cm have occurred. Grossly it appears as a well-circumscribed oval, fusiform-elongated, or disc-shaped mass, which may be lobulated. On sectioning the tissue is firm and homogeneous with cartilage-like consistency and pearl-grey colour.

Histopathology

Microscopically, desmoplastic fibroblastoma is relatively paucicellular with a prominent collagenous background. The tumour involves the subcutaneous fat in 70% of cases and extends into the skeletal muscle in 25% of cases. The margins are variably circumscribed. It is composed of scattered spindled or stellate-shaped fibroblasts and myofibroblasts. A minority of cases have variably, usually focally myxoid stromal change. The lesional blood vessels are usually inconspicuous with thin walls. Lower cellularity, lack of fascicular pattern, predomi-



Fig. 2.34 Desmoplastic fibroblastoma showing a 2;11 translocation with a breakpoint at 11q12.

nance of amorphous collagenous stroma and inconspicuous vasculature separate it from desmoid tumour.

Immunophenotype

The tumour cells are positive for vimentin and are variably positive for alpha-smooth muscle actin and occasionally for keratins AE1/AE3. They are negative for desmin, EMA, S100 protein and CD34 {1447}.

Genetics

Clonal chromosomal abnormalities have been observed in two cases {1911}. Both exhibited abnormalities involving band 11q12. Notably, an identical 2;11 translocation has also been observed in a case of fibroma of tendon sheath {440}.

Prognostic factors

These lesions do not recur and do not metastasize.



Fig. 2.31 Desmoplastic fibroblastoma. The lesion has a smooth, rounded contour.

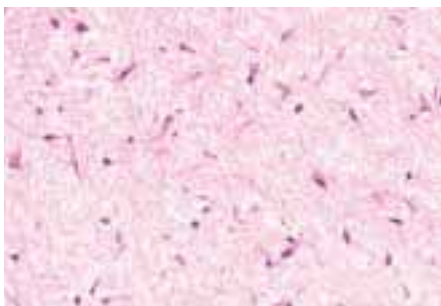


Fig. 2.32 Desmoplastic fibroblastoma. The tumour is paucicellular and composed of uniform, often stellate-shaped fibroblasts.

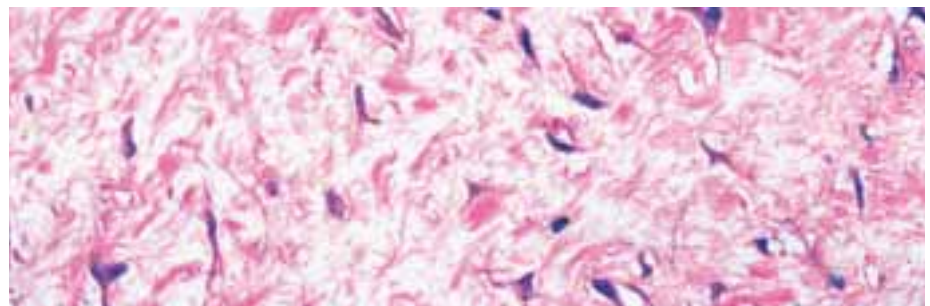


Fig. 2.33 Desmoplastic fibroblastoma. The tumour is paucicellular and composed of uniform, often stellate-shaped fibroblasts.

Mammary-type myofibroblastoma

M.E. McMenamin
J.A. Bridge

Definition

A benign mesenchymal neoplasm composed of spindle-shaped cells with features of myofibroblasts, embedded in a stroma that contains coarse bands of hyalinized collagen and conspicuous mast cells, and admixed with a variable amount of adipose tissue. The tumour is histologically identical to myofibroblastoma of breast.

ICD-O code 8825/0

Epidemiology

Lesions have arisen in adults with an age range of 35 to 67 years (median 55.5 years) and a male predilection (8 males, 2 females). The extramammary location of some myofibroblastomas has only recently been defined when 10 cases were reported {1382}. Therefore, conclusions related to epidemiology could alter with increased tumour recognition.

Sites of involvement

The most common location of mammary-type myofibroblastoma is the inguinal /

groin area. Other reported sites include abdominal wall, buttock, back and vaginal wall. Lesions arise most commonly in subcutaneous tissue; however, cases have arisen deep to abdominal wall muscle, in the posterior vaginal wall and in a paratesticular location. There is an apparent predilection for myofibroblastomas to arise along the putative anatomic "milk-line" that extends from axilla to medial groin.

Clinical features

The tumours generally present as either painless masses or incidental lesions that are detected during surgical procedures such as inguinal hernia repair. Occasional lesions are tender or painful. Tumours have been described to be present for up to a year before clinical presentation. There are no imaging data.

Aetiology

Unknown. It has been postulated that myofibroblastomas arising in the breast may be related to a patient's hormonal status, in that lesions are relatively com-

mon in older men, e.g. in the setting of gynaecomastia and anti-androgen therapy {1381,2217}. Mammary-type myofibroblastoma of soft tissue arises most commonly in older adult males. The apparent predilection for origin of myofibroblastomas along a putative milk-line suggests the possible existence of hormonally-responsive mesenchymal tissue.

Macroscopy

Reported lesions ranged in size from 2 to 13 cm (median 5.8 cm). The tumours are well circumscribed and firm. The colour can be variable (white, pink, tan or brown). The cut surface may be whorled or nodular. Soft "mucoïd"-appearing areas reflecting myxoid change were present in one case.

Histopathology

Tumours are unencapsulated but well circumscribed. They are composed of an admixture of spindle cells and adipose tissue and are morphologically identical to mammary myofibroblastoma {2217}. The spindle cells histologically resemble myofibroblasts and are characterized by oval to tapered nuclei with finely dispersed chromatin, small nucleoli, eosinophilic to amphophilic cytoplasm and poorly defined cytoplasmic borders. The spindle cells are frequently wavy in contour and generally are arranged in variably sized fascicles. The stroma is collagenous with broad bands of coarse hyalinized collagen that often adopt a zig-zag pattern. Stromal mast cells are usually numerous. Epithelioid change of the lesional cells and focal nuclear atypia with enlarged nuclei and multinucleation have been described {1382}. Such morphologic variation is well recognized in myofibroblastoma of breast {1381,2217}. The blood vessels in myofibroblastoma are generally not conspicuous, being small, often focally hyalinized and commonly having a perivascular lymphocytic infiltrate in contrast to the prominent medium to large vessels with markedly hyalinized walls

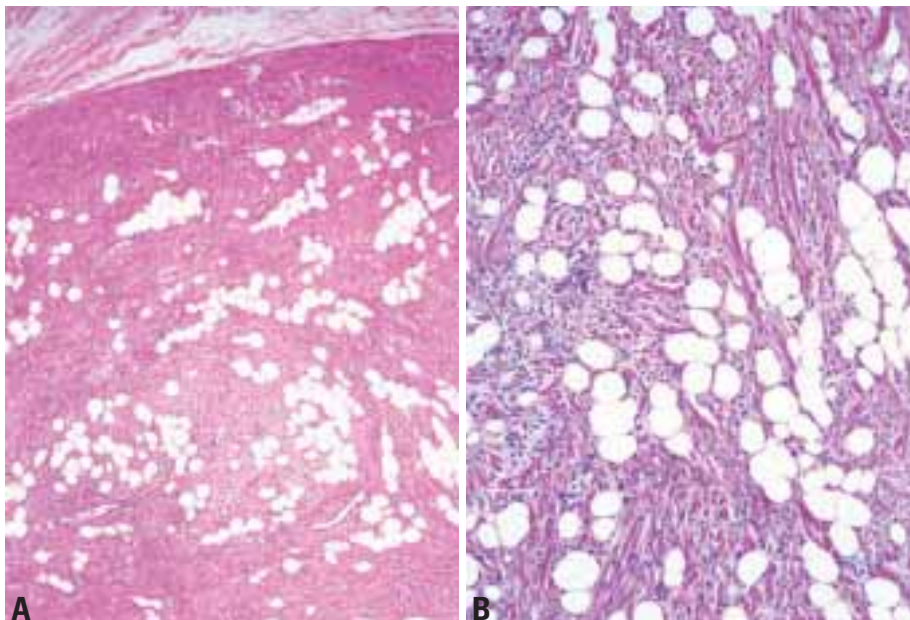


Fig. 2.35 **A** Mammary-type myofibroblastoma with sharply circumscribed margin. **B** Fascicles of spindle cells separated by coarse bands of intersecting hyalinized collagen. Note scattered adipose tissue.

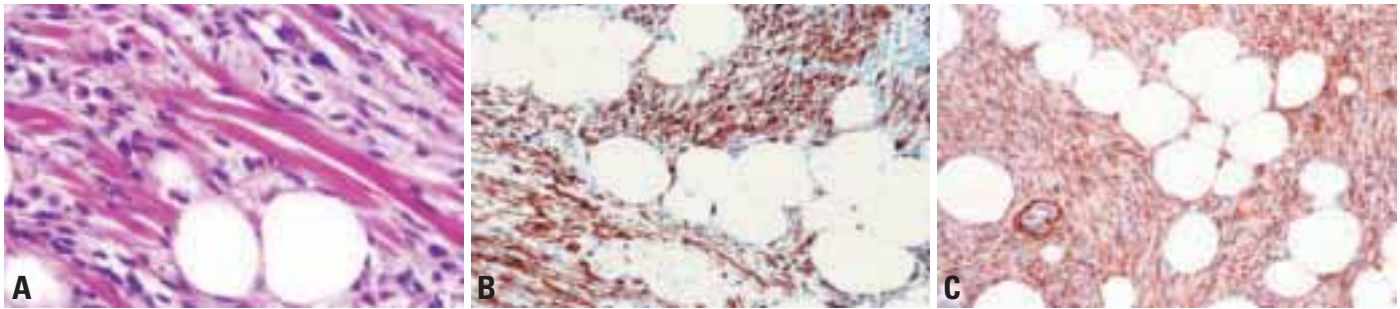


Fig. 2.36 Mammary-type myofibroblastoma. **A** Note the bland spindle cells with tapering nuclei, collagenous stroma and conspicuous mast cells. **B** The spindle cells are consistently immunopositive for desmin. **C** In most cases, the spindle cells are also positive for CD34.

that are characteristic in cellular angiofibroma or the large branching "haemangiopericytomatous" blood vessels that are seen in lipomatous haemangiopericytoma, two potential morphologic mimics. Mitotic figures range from 0-6 per 10 HPF.

Immunophenotype

As is characteristic of the breast counterpart, the typical immunophenotype of

extramammary myofibroblastoma is diffuse co-expression by the spindle cells of desmin and CD34. Expression of smooth muscle actin is seen in a third of cases.

Genetics

Partial monosomy 13q has been detected in two cases, as well as partial monosomy 16q in one of these two cases {1670}. Similar rearrangements of 13q

and 16q are characteristic of spindle cell lipoma {442}.

Prognostic factors

All tumours have followed a benign course following marginal local excision. However, the reported follow-up time is limited (up to 26 months).

Calcifying aponeurotic fibroma

G. Farshid

Definition

Calcifying aponeurotic fibroma (CAF) is a small tumour of the palms and soles of children with a propensity for local recurrence. Foci of calcification, palisaded round cells and radiating arms of fibroblasts characterise this lesion.

ICD-O code 8810/0

Synonym

Juvenile aponeurotic fibroma.

Epidemiology

CAF is very rare. The age range spans 0-64 with a median of 12 years. A slight male predisposition is found without familial or racial clustering. A case with multiple lesions has been reported {907}.

Sites of involvement

Palms, soles, wrists and ankles are typical sites of involvement. Back, arms, legs, neck and abdominal wall are rarely affected {657}. CAF arises near tendons, fascia and aponeuroses.

Clinical features

CAF presents as a solitary, small, slowly growing, poorly circumscribed non-tender mass. Plain X-rays show a soft tissue mass, possibly with stippled calcifications.

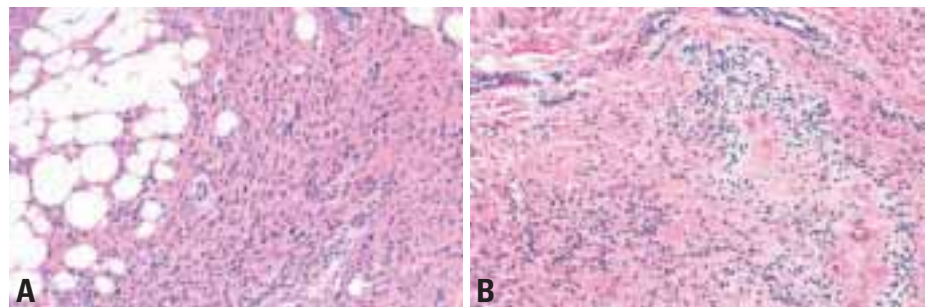


Fig. 2.37 Calcifying aponeurotic fibroma. **A** 1478 The spindle cell component resembles fibromatosis. **B** 1336 Paucicellular lesion with focal hyalinization.

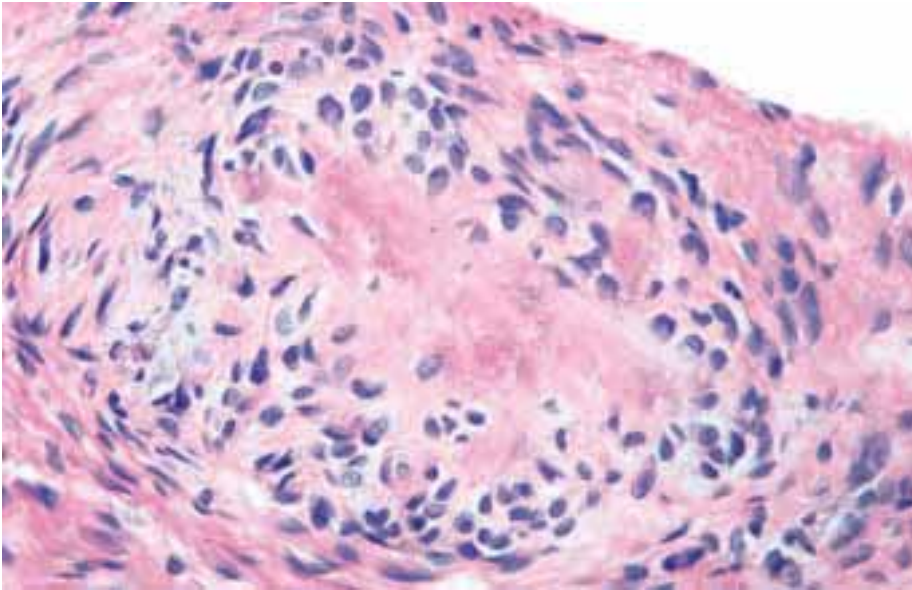


Fig. 2.38 Calcifying aponeurotic fibroma. Typical nodule with central hyalinization and incipient calcification.

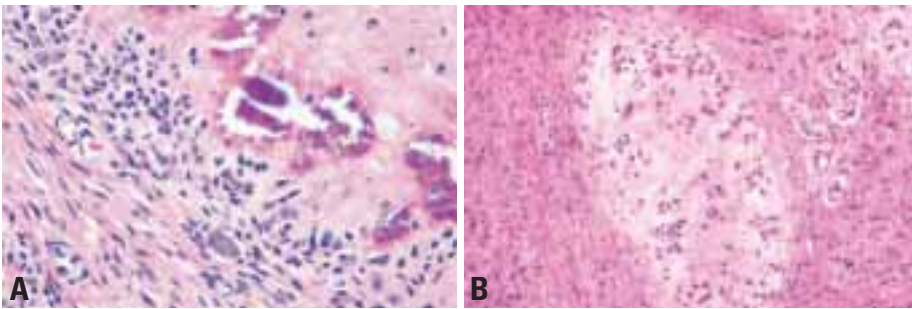


Fig. 2.39 Calcifying aponeurotic fibroma. **A** 1335 Calcification within a nodule. **B** 1489 Hyalinized area with chondroid features.

Macroscopy

CAF forms a firm, pale, infiltrative mass, usually <3 cm, with a gritty cut surface.

Histopathology

The typical lesion has two components: (1) nodular deposits of calcification, each surrounded by a palisade of round-

ed, chondrocyte-like cells, arranged in short, parallel arrays, (2) a less cellular, spindled, fibroblastic component between the coalescent calcified nodules and emanating into the surrounding soft tissues.

The stroma of nodules is usually hyalinized but may have chondroid features.

Osteoclastic giant cells may border the calcium. The lesion may engulf nerves and blood vessels. Degenerate nuclei may be present in the calcified areas but coagulative necrosis or numerous mitoses are not features of CAF {43, 657}.

An uncommon variant seen in very young children has a more diffuse growth pattern. Greater cellularity and a paucity of the mineralised matrix also characterise CAF in the very young.

Immunophenotype

The limited number of cases examined have variably expressed vimentin, smooth muscle actin, muscle specific actin, CD99 and S100 protein {657}.

Ultrastructure

Cells with features of chondrocytes, fibroblastic cells and occasional myofibroblastic cells are found on electron microscopy {1019}.

Prognostic factors

Up to 50% of patients experience local recurrence, usually within 3 years of diagnosis (range <1-9 yrs). This may be repeated but is not destructive or aggressive. Local recurrence is more likely in individuals <5 years of age but the likelihood of recurrence is not predictable on the basis of morphology, location or the completeness of the primary excision. The natural history of the lesion is one of reduced growth with age. Because local recurrence is not destructive, re-excision should be considered only for symptomatic relief and should conserve functionally important structures even if they are involved by tumour.

Angiomyofibroblastoma

C.D.M. Fletcher

Definition

A benign, well-circumscribed myofibroblastic neoplasm, usually arising in the pelviperineal region, especially the vulva, and apparently composed of stromal cells distinctive to this anatomic region. There may be morphologic overlap with cellular angiofibroma.

ICD-O code 8826/0

Epidemiology

Angiomyofibroblastoma is uncommon, having an incidence comparable to aggressive angiofibroma.

These tumours arise predominantly in females, principally in adults between menarche and menopause {687,738,1223,1564,1593}. Around 10% of patients are postmenopausal. Convincing examples have not been described before puberty. Rare cases occur in males {687,1593}.

Sites of involvement

Virtually all cases arise in pelviperineal subcutaneous tissue, with the majority arising in the vulva. Around 10-15% of cases are located in the vagina. Lesions in men occur in the scrotum or paratesticular soft tissue.

Clinical features

Most cases present as a slowly enlarging, painless, circumscribed mass. The most frequent preoperative diagnosis is Bartholin's gland 'cyst'. The aetiology is unknown.

Macroscopy

These lesions are well circumscribed but not encapsulated, with a tan/pink cut surface and a soft consistency. Necrosis is not seen. Most cases measure less than 5 cm in maximum diameter, although rare examples measuring up to 10 cm have been recognized.

Histopathology

Tumours are generally well demarcated by a thin fibrous pseudocapsule and, at low power, show varying cellularity with

prominent vessels throughout. Vessels are mostly small, thin-walled and ectatic and are set in an abundant loose, oedematous stroma. The tumour cells are round-to-spindle shaped with eosinophilic cytoplasm and typically are concentrated around vessels. Mitoses are rare. Binucleate and multinucleate

tumour cells are common. Some cases show very plasmacytoid or epithelioid cytomorphology and rare examples show degenerative ('ancient') nuclear hyperchromasia and atypia. Around 10% of cases have a variably prominent well differentiated adipocytic component. In post-menopausal patients the stroma is

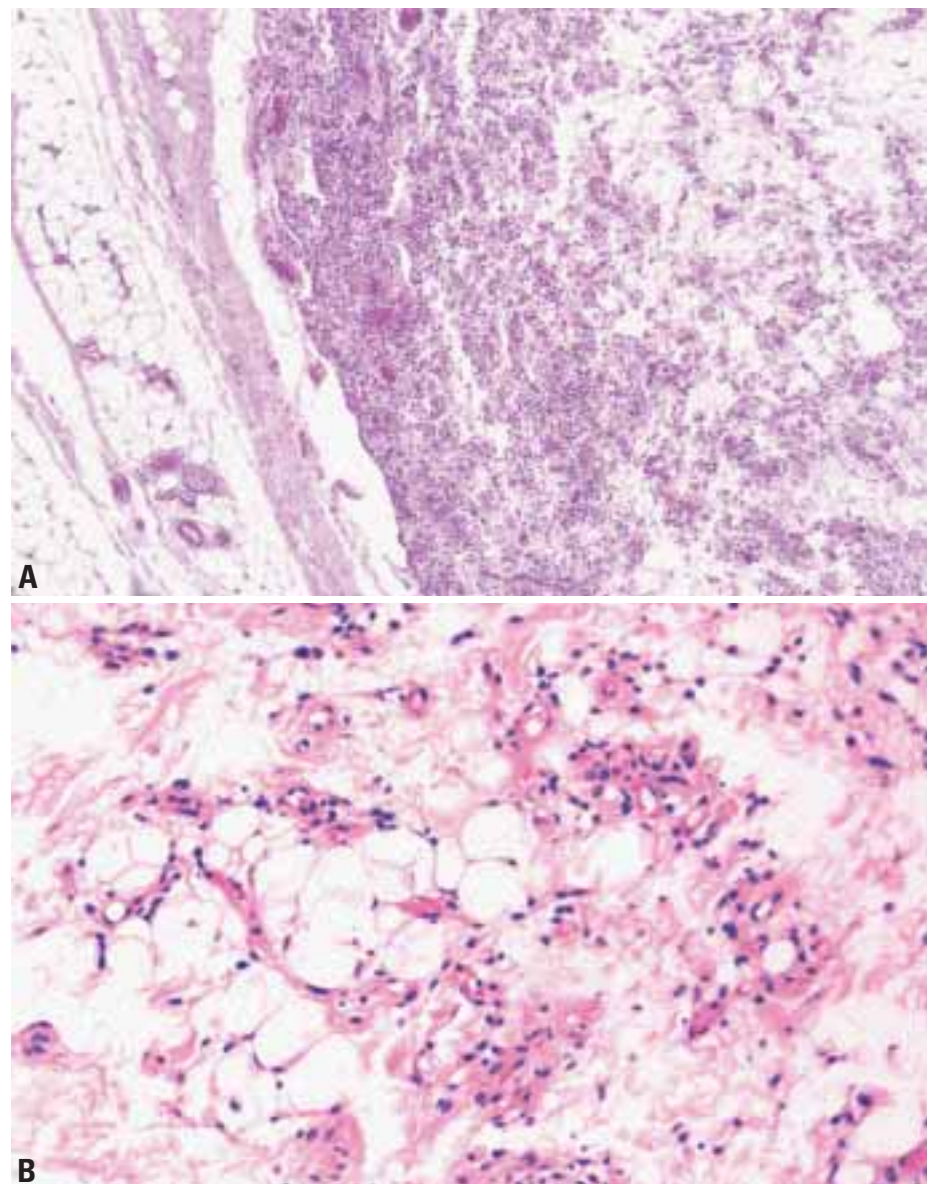


Fig. 2.40 Angiomyofibroblastoma. **A** A typically well demarcated tumour which **(B)** is more cellular and vascular than aggressive angiofibroma. Note the adipocytic component.

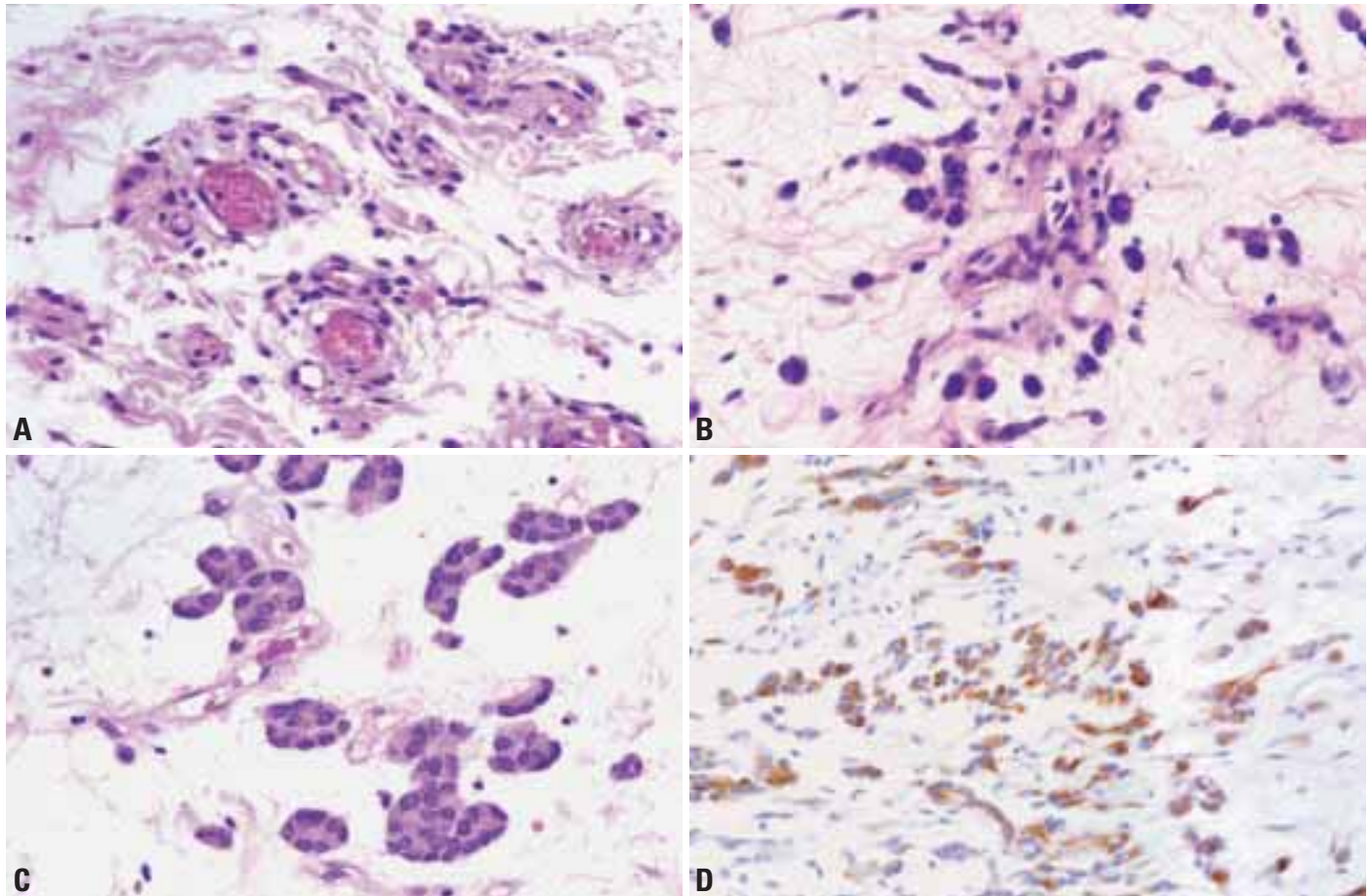


Fig. 2.41 Angiomyofibroblastoma. **A** Tumour cells and vessels are set in a loose oedematous stroma. **B** Binucleate and multinucleate cells are frequent and may have a plasmacytoid appearance. **C** In this example, the tumour cells are focally clustered with an epithelioid appearance. **D** Immunopositivity for desmin is a typical feature in most cases.

often less oedematous and more fibrous and there may be hyalinization of vessel walls. Some cases show morphologic overlap with cellular angiofibroma (see page 73) and rare cases show morphologic overlap with aggressive angiofibroma {826}.

Immunohistochemistry

The majority of cases show strong and diffuse desmin positivity, while, at most, there is usually only focal positivity for smooth muscle actin or pan-muscle actin

{687,1564,1593}. Desmin staining may be reduced or absent in postmenopausal cases. Tumour cells are consistently positive for oestrogen receptor and progesterone receptor {1223, 1593}, occasionally positive for CD34 and negative for S100 protein, keratin and fast myosin.

Ultrastructure

Tumour cells show fibroblastic or myofibroblastic features by electron microscopy {687,1564}.

Prognostic factors

Angiomyofibroblastoma is entirely benign and has never been reported to recur locally, even after marginal local excision. There is one reported case of a clinically malignant counterpart of angiomyofibroblastoma {1566}.

Cellular angiofibroma

W.B. Laskin

Definition

Cellular angiofibroma (CA) is a benign, highly cellular and richly vascularised mesenchymal neoplasm that usually arises in the superficial soft tissues of the vulva and in the inguinoscrotal region of men. The tumour may be related to angiofibromatoma, with which it shares certain morphological features.

ICD-O code 9160/0

Synonym

Male angiofibromatoma-like tumour {1222}.

Epidemiology

Cellular angiofibroma is a rare neoplasm that has been described in small series {1222,1585} and in case reports {393, 413,1216}. Cellular angiofibroma has a peak incidence in the fifth through seventh decades of life.

Sites of involvement

Although the vulva and inguinoscrotal region are classic locations for cellular angiofibroma, rare examples of tumours microscopically resembling cellular angiofibroma have been described in the retroperitoneum {1584}, perineum {1585}, and subcutaneous tissue of the chest {770}.

Clinical features

Patients usually present with a painless mass. In males, the mass may be associated with hernia or hydrocoele {1222}.

Aetiology

The aetiology is unclear. However, the immunohistochemical expression of estrogen and progesterone receptor proteins in a small number of cases {1216, 1222} suggests that these hormones may have a role in the pathogenesis of the neoplasm.

Macroscopy

Cellular angiofibroma of the vulva is generally small (less than 3 cm) {1585}, whereas cases in males tends to be larger in size (range, 2.5 to 14 cm) {1222}. The tumours appear as round, oval, or lobulated well-circumscribed nodules. The consistency of the lesion varies from soft to rubbery and the cut surface is solid with a grey-pink to yellow-brown colour.

Histopathology

The tumours are typically well circumscribed and may or may not possess a fibrous pseudocapsule. Cellularity is variable. The main proliferating element is a spindle cell with a cytologically-bland, oval to fusiform nucleus and a

scanty amount of lightly eosinophilic cytoplasm with ill defined borders. Epithelioid-appearing neoplastic cells are focally present in some examples . Cytological atypia has been reported in a few cases {1222,1585}. The tumour cells grow in vague fascicles or in a random fashion. Although mitotic rate can be brisk in cellular angiofibroma {1585}, mitotic activity in male cases is typically negligible {1222}. Atypical mitotic figures and necrosis are absent. The vascular component consists of numerous small

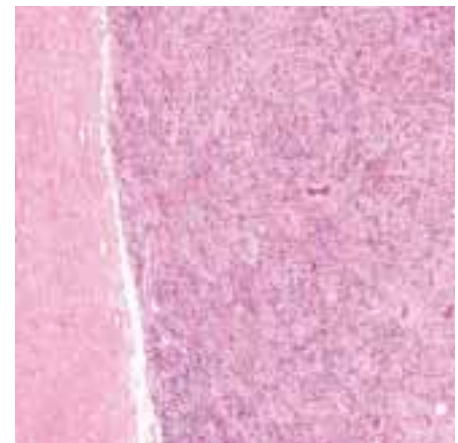


Fig. 2.42 Cellular angiofibroma is usually a well circumscribed neoplasm. A thick, fibrous pseudocapsule surrounds this example.

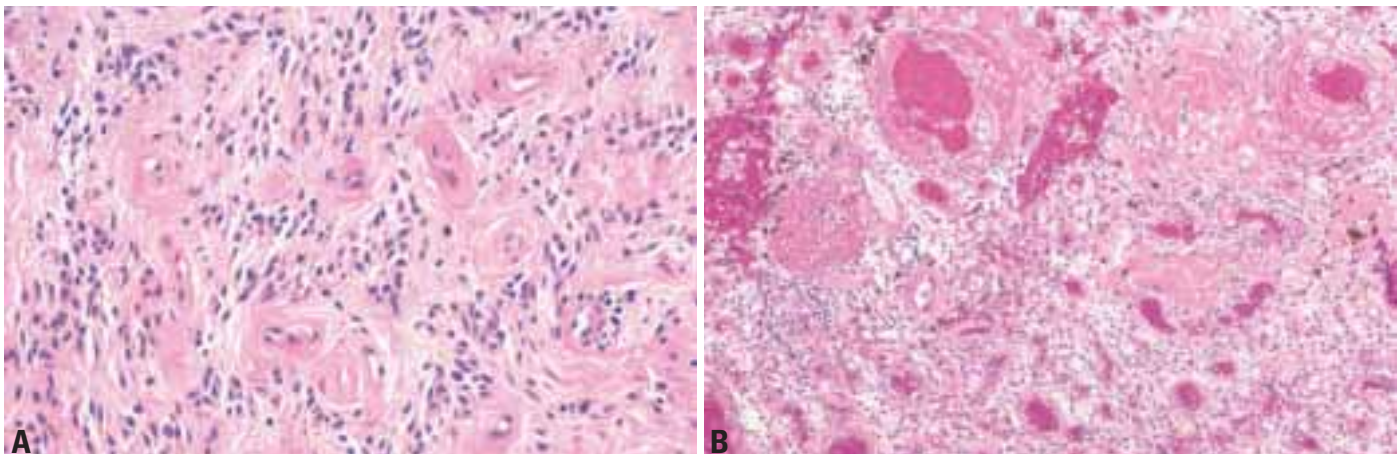


Fig. 2.43 Cellular angiofibroma. **A** The vascular component consists primarily of numerous small to medium-sized open vessels with hyaline walls. **B** Regressive and degenerative changes include organizing intraluminal thrombi, intramural inflammation, extravasated red blood cells, and haemosiderin deposits.

to medium-sized vessels distributed rather uniformly throughout the process. Perivascular hyaline fibrosis is present to some degree in all tumours. Intralesional fat in the form of small aggregates or individual adipocytes has been described in close to one-half of reported tumours {393,770,1222,1585} where it generally comprises less than 5% of the tumour area and is usually located near the periphery of the lesion. The stroma consists primarily of fine collagenous fibres. Additional stromal elements may include scattered thick bundles of eosinophilic collagen, a myxoid and oedematous stromal matrix, and hypocellular collagenous bands partitioning lesional tissue {1222}. Regressive or degenerative changes, including intravascular thrombi, extravasation of red blood cells and haemosiderin deposition, and cystic (pseudoangiomatous) stromal alteration are more common in males. Scattered mast cells are present in almost all tumours, whereas interstitial and perivascular chronic inflammation is more often noted in males.

Immunophenotype

The tumour cells show strong, diffuse expression of vimentin. CD34 expression has been documented in close to one-third of tumours tested {1216,1222,1585}. Although cellular angiofibroma in females has consistently been shown not to express actin(s) or desmin {393,413,770,1216,1585}, cases in males demonstrate more variable expression of muscle-specific and smooth muscle actin and desmin {1222}.

Prognostic factors

Although clinical follow-up data for CA is limited, only one case has been reported to recur {413,1216,1222,1585}. A complete (local) excision with uninvolved margins is adequate therapy for these benign neoplasms.

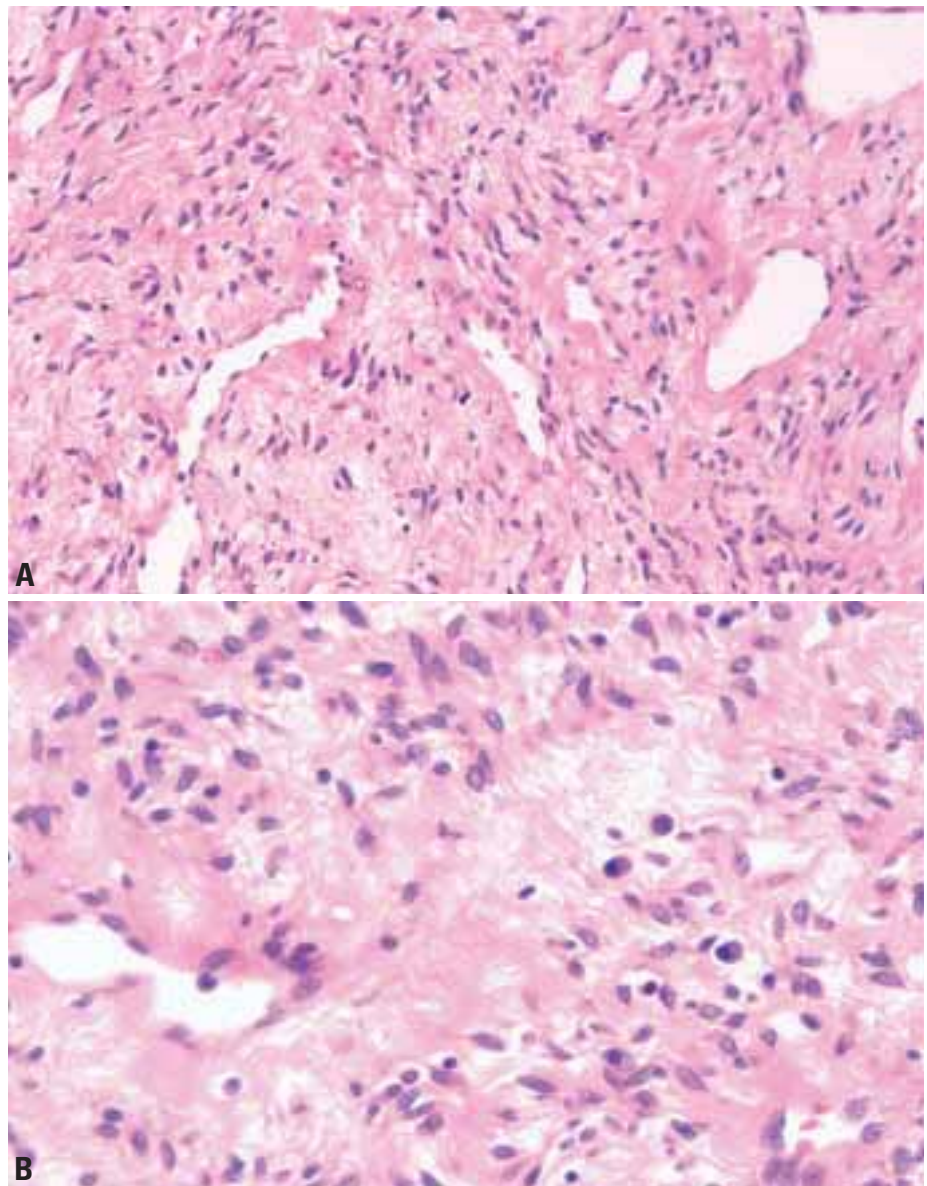


Fig. 2.44 Cellular angiofibroma. **A** Note the prominent dilated vessels with variably hyalinized walls and the short spindle cell fascicles. **B** The spindle cell cytomorphology is reminiscent of spindle cell lipoma. Note also the stromal mast cells.

Nuchal-type fibroma

M. Michal

Definition

Nuchal-type fibroma (NTF) is a rare benign hyalinized fibroblastic proliferation involving dermis and subcutis.

ICD-O code 8810/0

Synonym

Nuchal fibroma.

Epidemiology

NTF is significantly more common in men with a peak incidence during the third through fifth decades.

Sites of involvement

NTF typically affects the posterior neck region but can also occur in a number of other sites. Most of the extranuchal tumours are usually located in the upper back region, but other locations such as the face, extremities, and others can be encountered {600}. Because these extranuchal lesions are histologically indistinguishable from the nuchal examples, the designation nuchal-type fibroma was proposed to encompass all histologically similar lesions irrespective of their site of origin {1438}.

Clinical features

The mean greatest tumour dimension is slightly over 3 cm {1438}. It has hard consistency and white colour. The patients are usually asymptomatic. Interesting is the relationship between the patients with NTF and diabetes mellitus {11}. Up to 44% of patients with NTF in one series had diabetes mellitus {1438}.

Histopathology

NTF is an unencapsulated, poorly circumscribed, paucicellular lesion composed of thick, haphazardly arranged collagen fibres. In the central parts of the lesion, the collagen bundles intersect and form a vaguely lobular architecture. Compared with normal tissue from the nuchal area, NTFs show similarly thick collagen fibres. However, in NTF there is an expansion of collagenized dermis with encasement of adnexa, effacement of the subcutis with entrapment of adipocytes, and, in many cases, extension into the underlying skeletal muscle. A delicate network of elastic fibres is observed between the collagen fibres. Thus, NTFs appear to represent a local-

ized accentuation of the poorly cellular, collagenous connective tissue that normally resides in these sites. Scant numbers of lymphocytes are present in a minority of cases, but inflammatory features are never prominent. Many NTFs contain a localized proliferation of nerve twigs, similar to that seen in traumatic neuromas {113}, and in rare cases, there can be also perineurial fibrosis, as seen in Morton neuroma. These changes are probably the result of repetitive minor trauma or a response by small nerves to the local accumulation of collagen. NTF is histologically indistinguishable from Gardner fibroma (see below).

Immunophenotype

Immunohistochemically the lesions are vimentin, CD34 and CD99 positive and negative with antibodies to actins and desmin {526,1438,2337}.

Prognostic factors

NTF often recurs but does not metastasize.

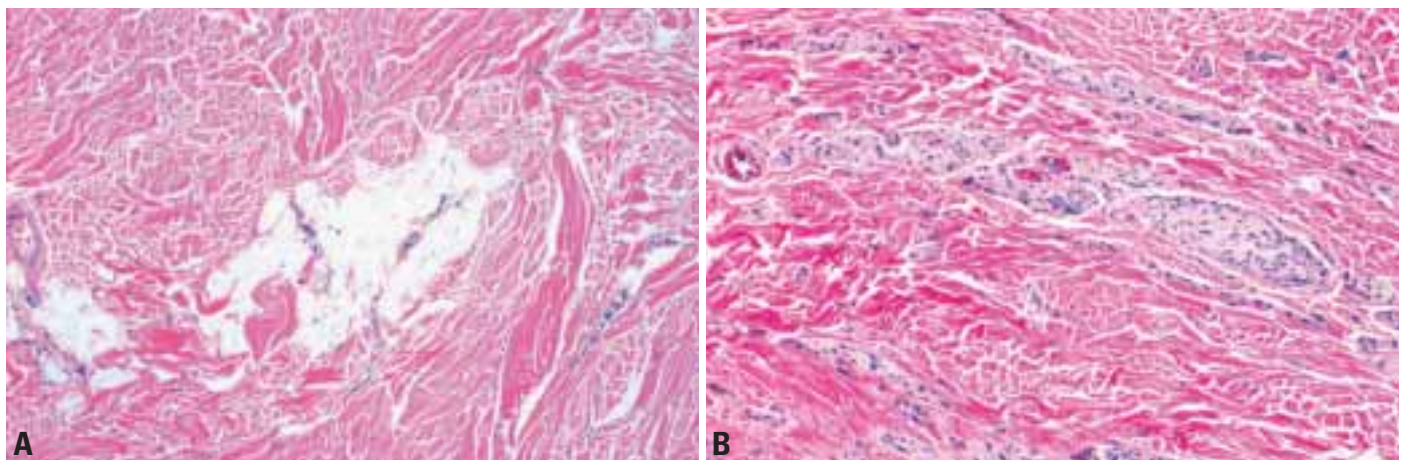


Fig. 2.45 Nuchal-type fibroma. **A** Entrapment of the adipose tissue by hypocellular collagenous tissue is a typical histological feature. **B** Note the tightly encased twigs of peripheral nerve.

Gardner fibroma

C.M. Coffin

Definition

Gardner fibroma is a benign soft tissue lesion consisting of thick, haphazardly arranged collagen bundles with interspersed bland fibroblasts, a plaque-like growth pattern with infiltration and entrapment of surrounding structures, and an association with desmoid-type fibromatosis and familial adenomatous polyposis / Gardner syndrome.

ICD-O code 8810/0

Epidemiology

Gardner fibroma is an uncommon soft tissue lesion. It affects predominantly infants, children, and adolescents. There is no sex predilection. Diagnosis of Gardner fibroma in early childhood can serve as the sentinel event for identifying Gardner syndrome kindreds and children with de novo *APC* germline mutations.

Sites of involvement

Gardner fibroma involves superficial and deep soft tissues of the paraspinal region, back, chest wall, flank, head and neck, and extremities {2227}. A similar mesenteric lesion has been reported as "desmoid precursor lesion" in patients with familial adenomatous polyposis {363}.

Clinical features

Patients with Gardner fibroma develop ill defined, plaque-like masses in superficial or deep soft tissue {2227}. The mass is usually asymptomatic, but may become painful with growth. Desmoid-type fibromatoses have arisen in the sites of Gardner fibromas {42,2227}. With imaging studies, Gardner fibroma appears as a dense plaque-like mass.

Macroscopy

Gardner fibroma ranges in size from 1 to 10 cm and involves superficial and deep soft tissues. The poorly circumscribed mass is firm, rubbery, and has a plaque-like appearance. The cut surface is white to tan-pink with scattered yellow areas representing entrapped adipose tissue {2227}.

Histopathology

The hypocellular proliferation of haphazardly arranged, coarse collagen bands contains scattered bland spindle cells and small blood vessels {2227}. The central portion of the lesion is uniform and displays a cracking artefact between the dense collagen bundles. Peripherally, the collagen extends into adjacent tissues and entraps fat, muscle, and nerves. A sparse mast cell infiltrate is present {2227}.

Immunophenotype

The spindle cells in Gardner fibroma are positive for vimentin and CD34 and negative for smooth muscle actin, muscle specific actin, desmin, oestrogen receptor, and progesterone receptor proteins {526,2226,2227}.

Genetic susceptibility

Among the reported cases of Gardner fibroma, more than 90% were associated with Gardner syndrome, familial adenomatous polyposis, and/or *APC* mutation.

Prognostic factors

45% of patients developed subsequent desmoid-type fibromatoses {42,2227}. Accurate identification of Gardner fibroma, especially in childhood, is critical for recognizing underlying Gardner syndrome, addressing the high risk of development of classic desmoid-type fibromatosis, and instituting early and close monitoring of the patient and other relatives for manifestations of adenomatous polyposis coli {2227}. Consideration should also be given to the diagnosis of Gardner fibroma in paediatric lesions resembling nuchal-type fibroma {42,2226,2227}.

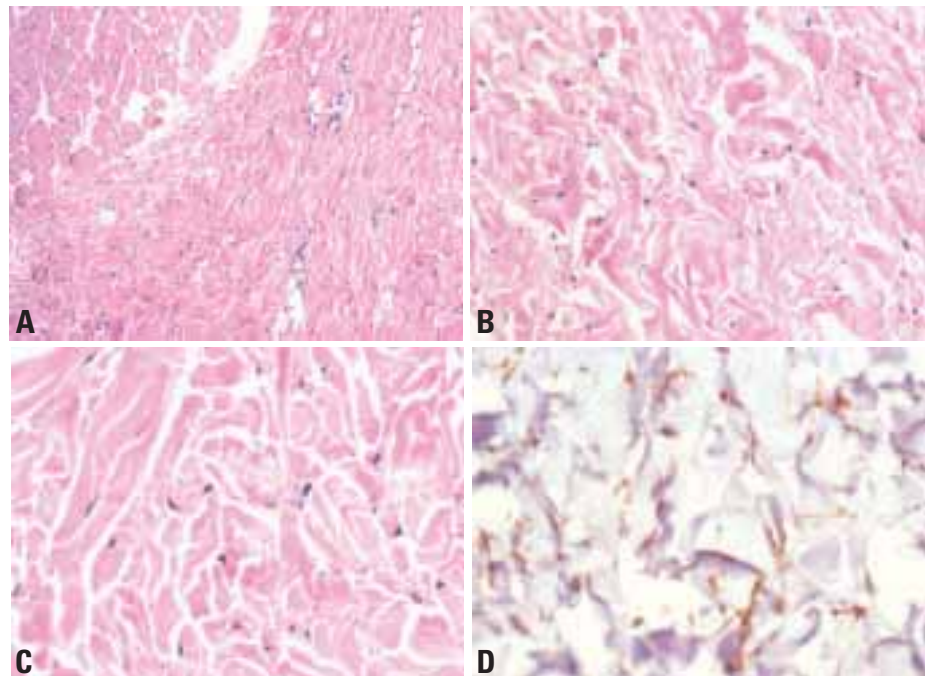


Fig. 2.46 Gardner fibroma. **A** Low power view of a paraspinal example in a young child showing a hypocellular fibrous lesion with entrapment of skeletal muscle and clusters of adipocytes. **B** Central areas of Gardner fibroma display hypocellular sheets of haphazardly arranged thick and thin collagen bands with sparse spindle cells. **C** Small bland spindle cells dispersed in cracks between collagen fibres. **D** CD34 staining identifies spindle cells between coarse collagen fibres.

Calcifying fibrous tumour

E. Montgomery

Definition

Calcifying fibrous tumour is a rare, benign fibrous lesion usually affecting children and young adults. It is paucicellular, with fibroblasts, dense collagenization, psammomatous and dystrophic calcification, and patchy lymphoplasmacytic infiltrates.

ICD-O code 8810/0

Synonyms

Childhood fibrous tumour with psammoma bodies {1809}, calcifying fibrous pseudotumour.

Epidemiology

Most soft tissue examples affect children and young adults without gender predilection {448,659,948,1306,1539}. Visceral examples usually occur in adults {157,337,868,1707}.

Sites of involvement

Tumours were originally described in the subcutaneous and deep soft tissues (extremities, trunk, neck, and scrotum) {659,1809} but have subsequently been reported all over the body, notably in the mesentery and peritoneum {157,337,1148,1539,1951,2256}, pleura (sometimes multiple) {606,868,1707}, mediastinum {557}, and adrenal gland {571}.

Clinical features

Soft tissue examples present as painless masses. Visceral examples may produce site-specific symptoms {157,868,1707}. Radiographs show well marginated, non-calcified tumours. Calcifications are apparent on CT and may be thick and band-like or punctate {606}. On MRI, masses appear similar to fibromatoses, with a mottled appearance and a signal closer to that of muscle than fat {659}.

Aetiology

Although examples have followed trauma {1707,2336} and have occurred in association with Castleman disease {448} and inflammatory myofibroblastic tumours {1714,2176}, the pathogenesis remains unknown.

Macroscopy

Tumours are well marginated but unencapsulated, ranging in size from <1 to 15 cm. Some show indistinct boundaries with infiltration into surrounding tissues. On occasion, a gritty texture is noted on sectioning, which reveals a firm whitish lesion.

Histopathology

Tumours consist of well circumscribed, unencapsulated, paucicellular, hyalinized fibrosclerotic tissue with a variable

inflammatory infiltrate consisting of lymphocytes and plasma cells. Lymphoid aggregates may be present. Calcifications, both psammomatous and dystrophic, are scattered throughout.

Immunophenotype

Lesional cells express vimentin and factor XIIIa, but usually lack actins, desmin, factor VIII, S100 protein, neurofilament protein, cytokeratins, CD34, and CD31. The immunophenotype differs from that of inflammatory myofibroblastic tumours in that most calcifying fibrous tumours



Fig. 2.47 Fat suppressed, gadolinium-enhanced T1 MRI of a calcifying fibrous tumour.

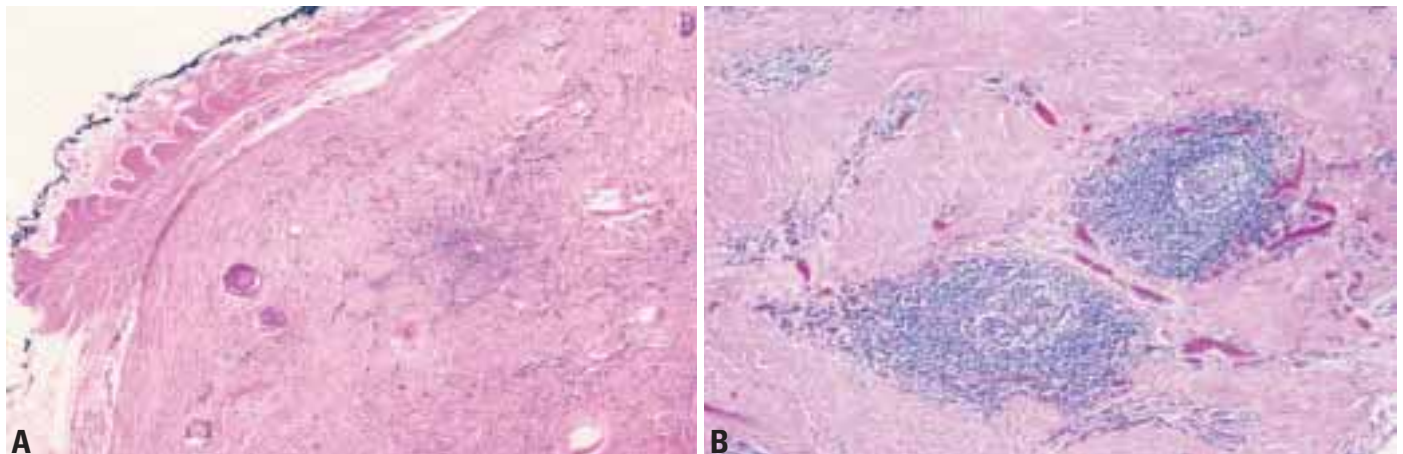


Fig. 2.48 **A** Calcifying fibrous tumour. The lesion is well marginated but not encapsulated. Note the psammomatous calcifications. **B** 530 Lymphoid follicles in this calcifying fibrous tumour.

lack actin and anaplastic lymphoma kinase (ALK) {948,1951}. Occasional lesions have expressed CD34 {948, 2256}.

Ultrastructure

On electron microscopy, fibroblasts are accompanied by collagen fibrils. The dystrophic and psammomatous calcifications are observed as electron-dense amorphous masses and laminated bodies, respectively, within the cytoplasm of fibroblasts and in the collagenous stroma. Cytoplasmic degeneration may be an initial event in intracytoplasmic calcification; extracellular calcified material often abuts fibroblasts {1306,1707}.

Prognostic factors

These lesions are benign; occasional recurrences are recorded and may be repeated {659,948}.

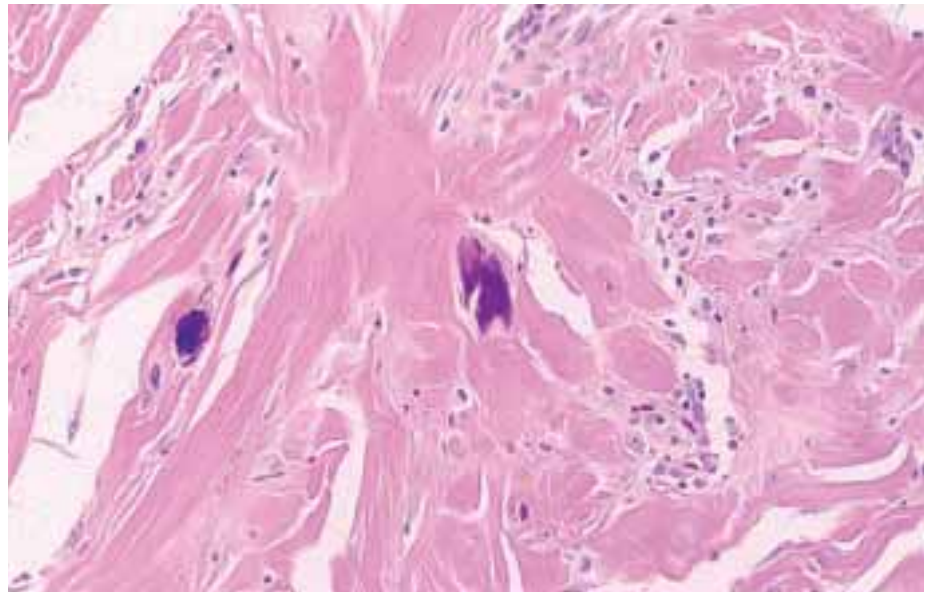


Fig. 2.49 Calcifying fibrous tumour. Calcifications are seen in a background with dense collagen and scattered plasma cells.

Giant cell angiofibroma

L. Guillou
J.A. Bridge

Definition

A non-recurring, benign neoplasm containing multinucleated giant stromal cells and angiectoid spaces. Giant cell angiofibroma may belong to the solitary fibrous tumour group.

ICD-O code 9160/0

Epidemiology

Described in 1995 {491}, giant cell angiofibroma (GCA) is a distinctive benign neoplasm which most often involves the orbital region and eyelids of middle-aged adults (median age : 45 years). Orbital GCA predominates in

males {491,912}, whereas extraorbital lesions predominate in female patients {853,2109}.

Sites of involvement

GCA is usually observed in the orbital region, including the eyelids, the nasolacrimal duct and the lacrimal sac region {491,912}. It has also been observed in the head and neck region outside the orbit (scalp, retroauricular region, parotid gland, cheek, submandibular region, buccal mucosa), as well as in the posterior mediastinum {740}, back, axillary and inguinal regions, retroperitoneum, and vulva {491,853,1454,2109}. Most

extraorbital lesions are located subcutaneously.

Clinical features

GCA usually presents clinically as a slowly growing, sometimes painful {2109} mass.

Macroscopy

Grossly, GCAs are well circumscribed, variably encapsulated, small (median : 3 cm) lesions. Upon section, haemorrhagic and/or cystic changes may be observed. Soft tissue lesions tend to be larger than orbital-region tumours, sometimes measuring up to 10 cm {1950,2109}.

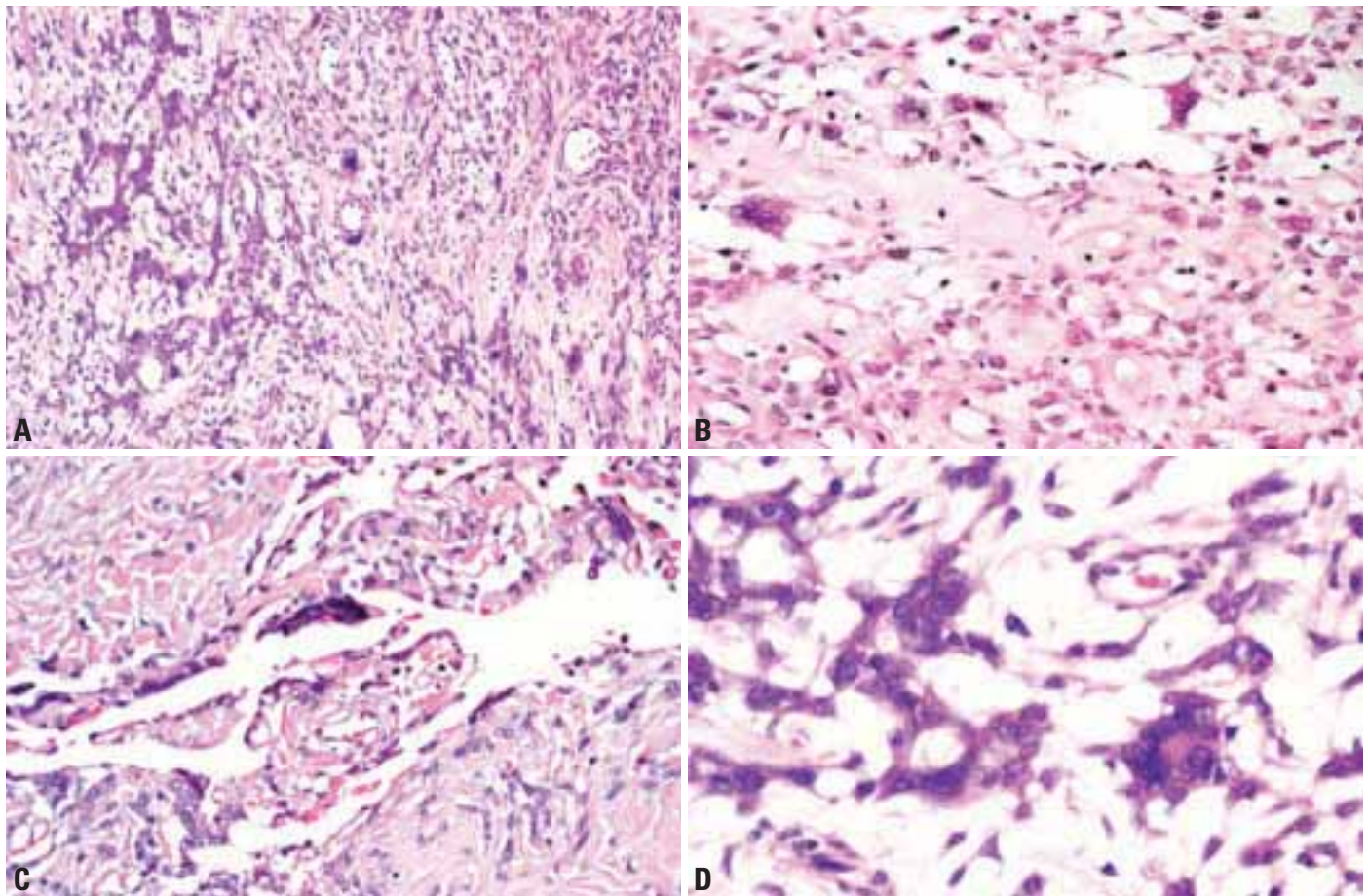


Fig. 2.50 **A** A giant cell angiofibroma of the vulva presenting as a well-circumscribed nonencapsulated mass. **B** Giant cell rich areas often contain characteristic medium-sized to small thick-walled vessels. **C** Multinucleated giant cells lining pseudovascular spaces in giant cell angiofibroma. **D** Morphological appearance of multinucleated giant stromal cells in giant cell angiofibroma.

Histopathology

The tumour displays a varying combination of cellular areas composed of bland round to spindle cells, collagenous or myxoid stroma with focal sclerotic areas, medium-sized to small thick-walled vessels, and multinucleated giant stromal cells, often lining angiectoid spaces {491,853,912,2109}. The number of giant cells may vary from one tumour to another, and pseudovascular spaces may occasionally be absent.

Immunophenotype

Mononuclear and multinucleated stromal cells are characteristically positive for

CD34, CD99 and, less frequently, BCL2 {853,2109}.

Genetics

Cytogenetic analysis of one case arising in the orbit revealed abnormalities of chromosome band 6q13 {1988}.

Prognostic factors

Nearly all GCA show benign behaviour; recurrences after complete excision are exceptional {491,853,2109}.

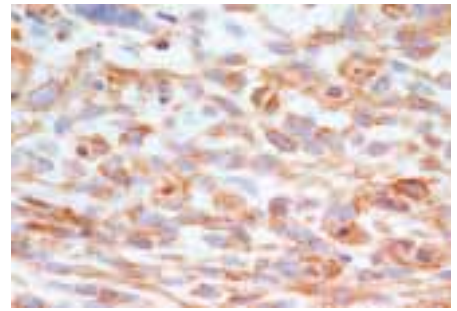


Fig. 2.51 Strong immunoreactivity of mono- and multinucleated stromal cells for CD34.

Superficial fibromatoses

J.R. Goldblum
J.A. Fletcher

Definition

Superficial fibromatoses are fibroblastic proliferations that arise in the palmar or plantar soft tissues and are characterized by infiltrative growth. They have a tendency toward local recurrence but do not metastasize.

ICD-O code

Palmar / plantar fibromatosis 8821/1

Synonyms

Palmar fibromatosis: Dupuytren disease, Dupuytren contracture.
Plantar fibromatosis: Ledderhose disease.

Epidemiology

Palmar fibromatosis tends to affect adults with a rapid increase in incidence with advancing age. Rarely, patients younger than 30 years of age are affected. The condition is three to four times more common in men and is most common in Northern Europe and in those parts of the world now settled by Northern Europeans {1455}. These lesions are quite rare in non-Caucasian populations {1478}. In contrast, plantar lesions have a much greater incidence in children and adolescents {45}. Although plantar lesions arise more commonly in men, the gender difference is not as great as that found in palmar lesions. Both forms of

fibromatosis have been linked with numerous other disease processes including other forms of fibromatosis. Approximately 5% to 20% of palmar fibromatoses are associated with plantar lesions, and up to 4% of patients also have penile fibromatosis (Peyronie disease) {195}.

Sites of involvement

Palmar lesions occur on the volar surface of the hand with a slight predilection for the right palmar surface. Almost 50% of cases are bilateral. Plantar lesions arise within the plantar aponeurosis, usually in non-weight-bearing areas. Cases arising in children tend to occur in the antero-medial portion of the heel pad {799}.

Clinical features

For palmar lesions, the initial manifestation is typically that of an isolated firm palmar nodule that is usually asymptomatic and which ultimately results in cord-like indurations or bands between multiple nodules and adjacent fingers. This often leads to puckering of the overlying skin, and flexion contractures principally affecting the 4th and 5th digits. Plantar lesions present as a firm subcutaneous nodule or thickening that adheres to the skin and is frequently associated with mild pain after long

standing or walking. Plantar lesions only exceptionally result in contraction of the toes {366}.

Aetiology

The pathogenesis is multifactorial and includes a genetic component, as many patients have a significant family history of this disease {1271}. Trauma likely also has a central role. The coexistence of these diseases with epilepsy, diabetes and alcohol-induced liver disease suggests that factors other than trauma are also important.

Macroscopy

Both lesions consist of small nodules or an ill defined conglomerate of several nodular masses intimately associated with the aponeurosis and subcutaneous fat. On cut section, both have a grey-yellow or white surface, although the colour depends on the collagen content of the lesion.

Histopathology

The proliferative phase is characterized by a cellular proliferation of plump, immature-appearing spindled cells that vary little in size and shape, have normochromatic nuclei and small pinpoint nucleoli. Plantar lesions are often notably hypercellular. Mitotic figures are usually

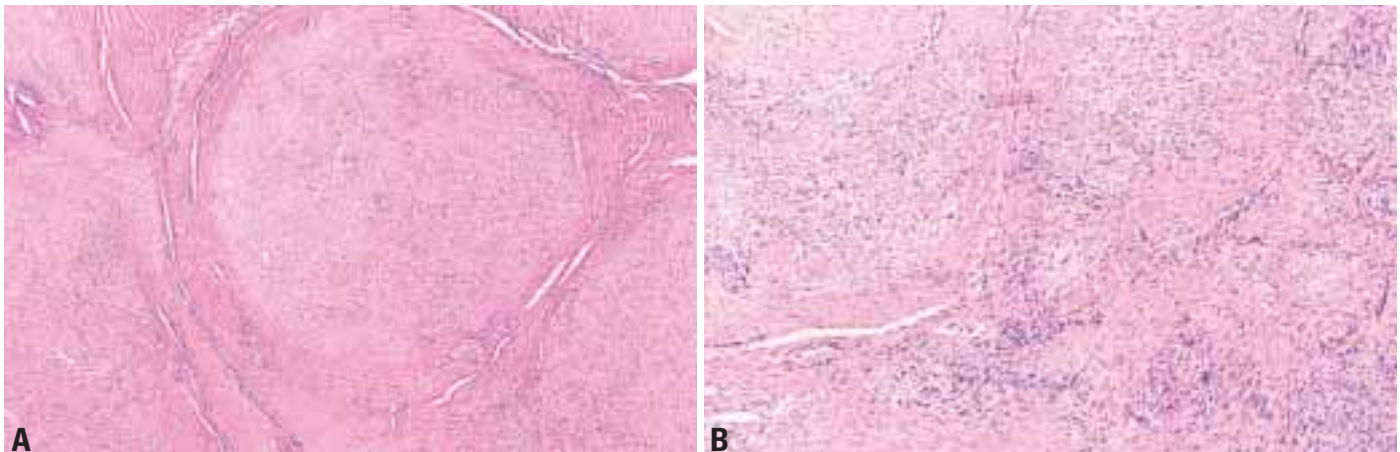


Fig. 2.52 **A** Low power view showing typically multinodular growth pattern (within tendoaponeurotic fibrous tissue), as is usually seen in plantar lesions. **B** In the early (proliferative) phase, palmar fascial or aponeurotic tissue is expanded by hypercellular spindle cell nodules.

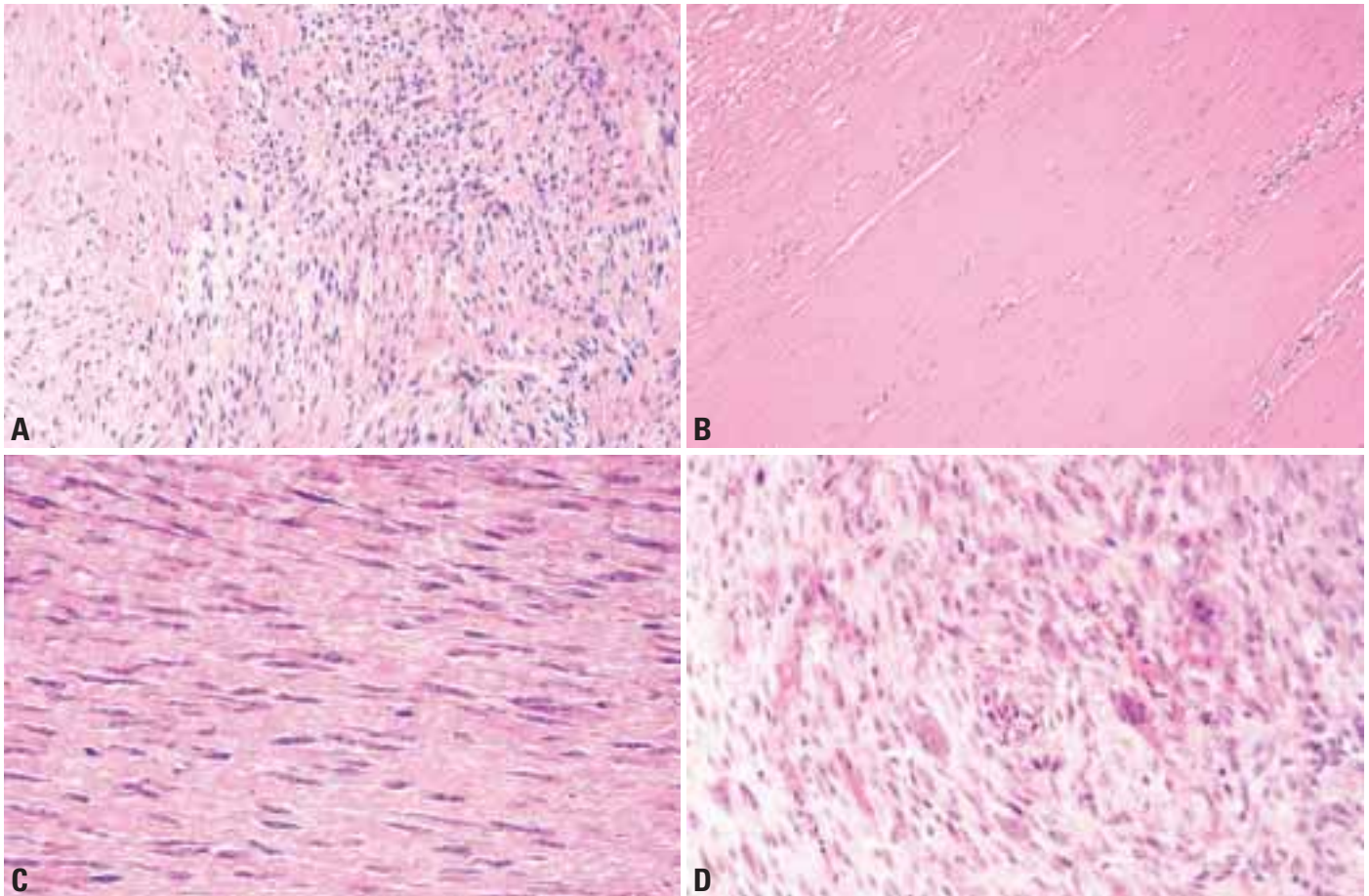


Fig. 2.53 **A** Early (proliferative) lesion of palmar fibromatosis showing bland fibroblastic / myofibroblastic cells. **B** Palmar fibromatosis. Late lesions associated with contracture consist largely of densely hyalinized hypocellular collagenous tissue. **C** High magnification view of cytologically bland cells in a palmar fibromatosis. In this example, the cells are widely separated by collagen. **D** Plantar fibromatosis may contain scattered osteoclastic giant cells.

infrequent but may be focally prominent, but the latter is not indicative of malignancy (e.g. fibrosarcoma). Cells are intimately associated with moderate amounts of collagen and elongated vessels. Older lesions are considerably less cellular and contain increased amounts of dense collagen. Occasional cases of plantar fibromatosis contain notable multinucleate giant cells [623].

Immunophenotype

The cells strongly express vimentin and variably stain for muscle-specific and smooth muscle actin, depending upon

the stage and degree of myofibroblastic differentiation.

Ultrastructure

Most cells have the features of fibroblasts, although a proportion of the cells has myofibroblastic features.

Genetics

Chromosome aberrations have been described in more than 50 cases, all showing near-diploid karyotypes. Simple numerical changes are typical, particularly gain of chromosomes 7 or 8 [1477].

Prognostic factors

Risk of local recurrence is most closely related to the extent of surgical excision. Dermofasciectomy followed by skin grafting is associated with the lowest rate of local recurrence [275,873]. For plantar lesions, there appears to be an increased risk of local recurrence in those cases with multiple nodules, in patients with bilateral lesions, those with a positive family history and those who develop a postoperative neuroma [49,2216].

Desmoid-type fibromatoses

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J.A. Fletcher

Definition

Desmoid-type fibromatoses are clonal fibroblastic proliferations that arise in the deep soft tissues and are characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize.

ICD-O codes

Aggressive fibromatosis 8821/1
Abdominal (mesenteric) fibromatosis 8822/1

Synonyms

Aggressive fibromatosis, musculoaponeurotic fibromatosis, desmoid tumour.

Epidemiology

Deep fibromatoses are rarer than their superficial counterparts and are encountered in two to four individuals per million population per year {1779}. In the paediatric population, these lesions have an equal sex incidence and most are extra-abdominal. Patients between puberty and 40 years of age tend to be female, and the abdominal wall is the favoured site in this group. Later in adulthood, these tumours are equally distributed between abdominal and extra-abdominal locations and occur equally in both genders {914}.

Sites of involvement

Extra-abdominal fibromatoses may be located in a variety of anatomic locations, although the principal sites of involvement are the shoulder, chest wall and back, thigh and head and neck. Abdominal tumours arise from musculoaponeurotic structures of the abdominal wall, especially the rectus and internal oblique muscles and their fascial coverings. Intra-abdominal fibromatoses arise in the pelvis or mesentery.

Clinical features

Extra-abdominal fibromatoses typically arise as a deep-seated, firm, poorly circumscribed mass that has grown insidiously and causes little or no pain. Some cases are multifocal. Although rare,

some lesions cause decreased joint mobility or neurological symptoms. Abdominal wall lesions typically arise in young, gravid or parous women during gestation or, more frequently, during the first year following childbirth. Pelvic fibromatoses arise as a slowly growing palpable mass that is usually asymptomatic and is often mistaken for an ovarian neoplasm. Mesenteric lesions may be sporadic or arise in patients with Gardner syndrome. Most patients present with an asymptomatic abdominal mass, but some have mild abdominal pain. Less commonly, patients with mesenteric lesions present with gastrointestinal bleeding or an acute abdomen secondary to bowel perforation.

Aetiology

The pathogenesis is multifactorial and includes genetic, endocrine and physical factors. Features suggesting an underlying genetic basis include the existence of familial cases and the pres-

ence of these lesions, particularly mesenteric fibromatoses, in patients with Gardner syndrome {859}. Endocrine factors are implicated by the frequent occurrence of abdominal lesions during or after pregnancy. Trauma likely also serves as a contributory cause.

Macroscopy

These lesions are firm and cut with a gritty sensation. On cross section, the cut surface reveals a glistening white, coarsely trabeculated surface resembling scar tissue. Lesions in the abdomen may appear well circumscribed. Most tumours measure between 5 and 10 cm.

Histopathology

These lesions are typically poorly circumscribed with infiltration of the surrounding soft tissue structures. All are characterized by a proliferation of elongated, slender, spindle-shaped cells of uniform appearance, set in a collage-

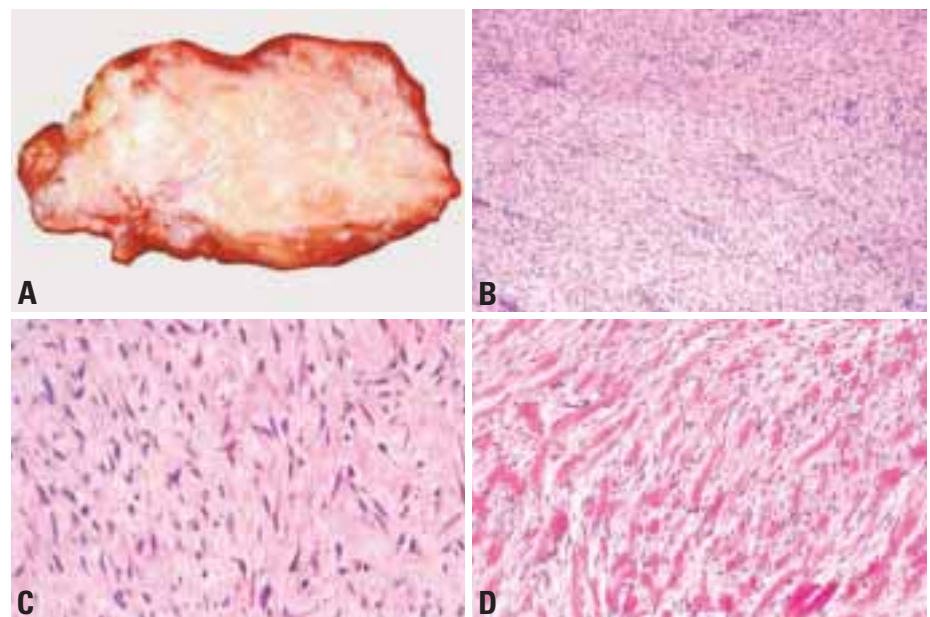


Fig. 2.54 Extra-abdominal desmoid fibromatosis. **A** Note the whorled fibrous cut surface and poorly defined margins to surrounding skeletal muscle. **B** Cellular proliferation of bland spindle cells arranged into ill defined long fascicles. Regularly distributed blood vessels are evident. **C** Cells are spindled or stellate in shape and have bland nuclear features. **D** Extensive keloid-like collagen deposition.

nous stroma containing variably prominent vessels, sometimes with perivascular oedema. The cells lack hyperchromasia or atypia and have small, pale-staining nuclei with 1 to 3 minute nucleoli. Cells are usually arranged in sweeping bundles. As with superficial fibromatoses, the mitotic rate is variable. Keloid-like collagen or extensive hyalinization may be present. Some lesions, particularly those arising in the mesentery and pelvis, have extensive stromal myxoid change and may show more fasciitis-like cytomorphology.

Immunophenotype

The cells strongly express vimentin and variably stain for muscle-specific and smooth muscle actin. Rare cells may also express desmin and S100 protein.

Ultrastructure

Most cells have the features of fibroblasts, although a proportion of the cells have myofibroblastic features.

Genetics

Desmoid-type fibromatoses may contain cell subpopulations with trisomies for chromosomes 8 and/or 20 {251,267,433,476,689,1986}. These numerical chromosomal aberrations are typically found in no more than 30% of the fibromatosis cells, and it is unlikely that they play a crucial role at the inception of the tumours {267,476,689}. Some clinical series suggest a relationship between the trisomies and more advanced disease, but there is no consensus that any of these aberrations are prognostic in patients with newly-diagnosed fibromatoses {438,444,476,689, 1161,1431}. Inactivation of the *APC* tumour suppressor on chromosome arm 5q, occurring typically by point mutation or allelic deletion, is a potential initiating event in

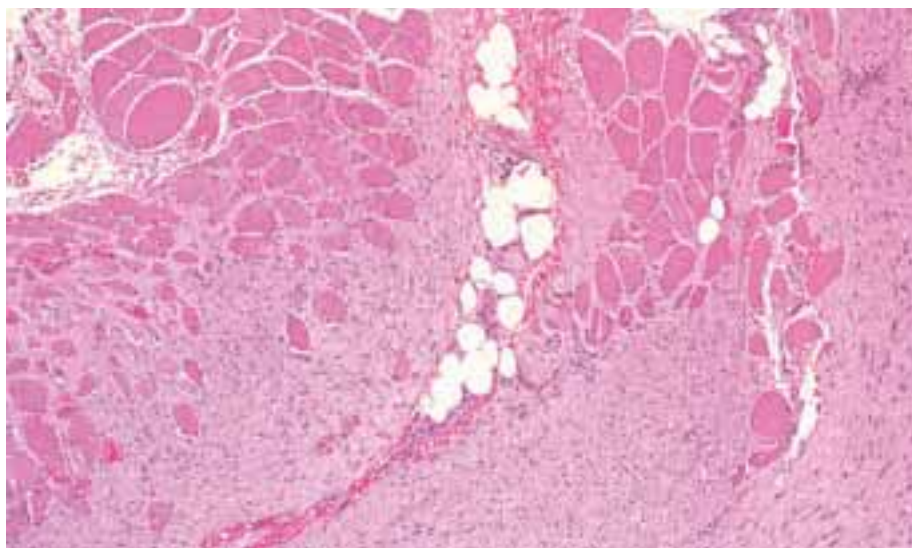


Fig. 2.55 Desmoid fibromatosis. Note the irregular infiltration into adjacent skeletal muscle and adipose tissue.

desmoid tumours. However, *APC* inactivation is found primarily in desmoid tumours from patients with familial polyposis, and is less common in patients with sporadic desmoid tumours {261,447,785,1481,1640,1919,2327}. Germ-line *APC* mutations can result in familial desmoid tumour syndromes in which the polyposis component is either inconspicuous or even absent.

The *APC* protein binds to beta-catenin, which is an important cell signalling protein in the Wnt pathway. *APC* binding to beta-catenin induces a chain of events leading to degradation of beta-catenin, and inhibition of Wnt pathway signalling {1649,1819,1820}. Many sporadic desmoid tumours contain activating beta-catenin mutations, which render beta-catenin resistant to the normal inhibitory influence of *APC* {46,1249}. These beta-catenin activating mutations are generally "either/or" in relationship to *APC* inactivating mutations {9,1483,

1841,2101}. Because both types of mutation are manifested by stabilization of the beta-catenin protein, these molecular mechanisms can be addressed at a screening level by immunohistochemical staining for beta-catenin. Beta-catenin is strongly expressed in most desmoid tumours {9,1483}. Other distinctive genetic features, that distinguish desmoid tumours from most fibrosarcomas, include a paucity of *BCL2*, *RB1*, and *TP53* aberrations {966}.

Prognostic factors

Local recurrence is frequent and most closely related to the adequacy of surgical excision. However, attempts to achieve tumour-free resection margins may result in significant morbidity {1246,1420}. Some cases may recur as a consequence of multicentricity. Despite the lack of metastatic potential, some desmoids prove fatal due to local effects, especially in the head and neck region.

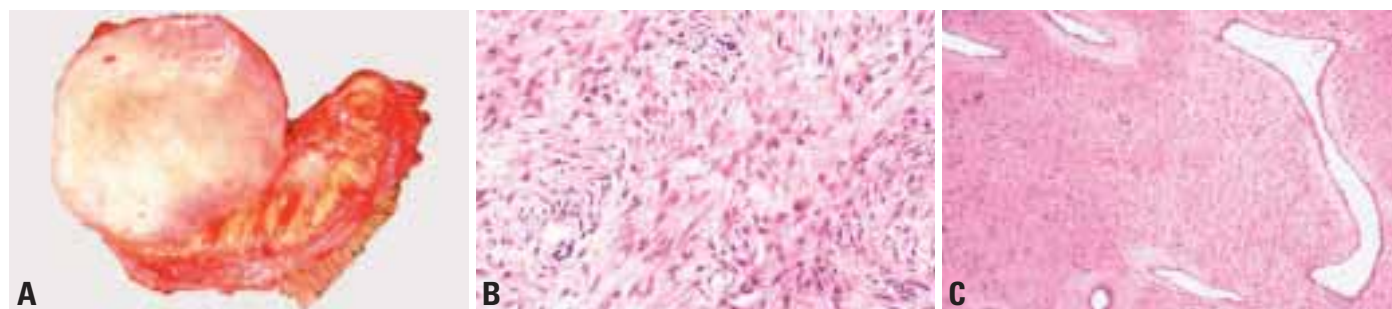


Fig. 2.56 **A** Mesenteric desmoid fibromatosis, presenting as a typically large, macroscopically circumscribed mass. The cut surface of mesenteric examples is often myxoid. **B** Mesenteric fibromatosis with extensive myxoid change. **C** Ectatic blood vessels with perivascular hyalinization in a mesenteric fibromatosis.

Lipofibromatosis

M.M. Miettinen
J.F. Fetsch

Definition

A histologically distinctive fibrofatty tumour of childhood, previously designated as infantile fibromatosis of non-desmoid type, with predilection for distal extremities.

Synonyms

Infantile fibromatosis, non-desmoid type.

Clinical features

This rare paediatric tumour was recently reported by Fetsch et al. [658]. It typically forms an ill defined slowly growing, painless mass in hands and feet and rarely occurs in the thigh, trunk and head. The tumour has been described exclusively in children from infancy to the early second decade and in some cases has been congenital; the median age for first surgery is 1 year. There is an over 2:1 male predominance.

Macroscopy

Grossly the lesion is yellowish or whitish tan, with a fatty component typically evident. It usually measures 1-3 cm and rarely exceeds 5 cm, with a median size of 2 cm.

Histopathology

Microscopically the tumour is composed of alternating streaks of mature adipose tissue and a fibrous spindle cell component mainly involving the septa of adipose tissue. This constellation resembles that of fibrous hamartoma of infancy, except that there is no primitive oval cell

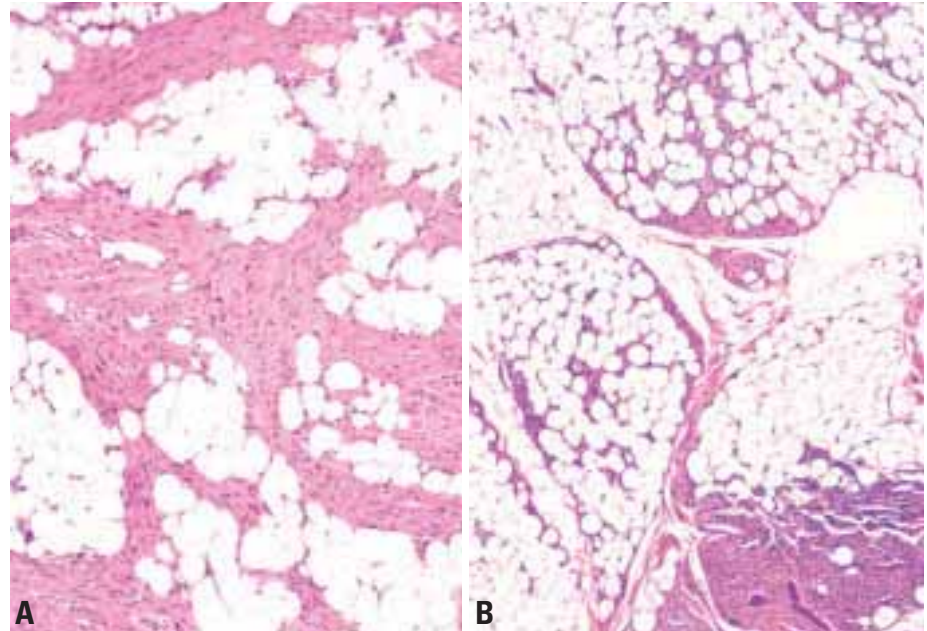


Fig. 2.57 Lipofibromatosis. **A** Even admixture of fibroblastic and adipocytic components. **B** The relative proportion of the two components is variable and the spindle cell areas may form delicate trabeculae.

component with myxoid stroma. The lesion differs from other forms of fibromatosis by the architectural preservation of fat and lack of solid fibrous growth. Mitotic activity is low and nuclear atypia is absent. Many cases contain minute collections of small vacuolated cells near the interface between the fibroblastic element and the mature adipocytes.

Immunophenotype

The spindle cells are often focally positive for CD34, BCL2, S100 protein, actins

and EMA and may also be positive for CD99. No reactivity has been detected for desmin and keratins.

Prognostic factors

The tumour has a high rate of non-destructive local recurrence, but there is no metastatic potential. Congenital onset, male sex, mitotic activity in the fibroblastic component and incomplete excision may be risk factors for recurrence.

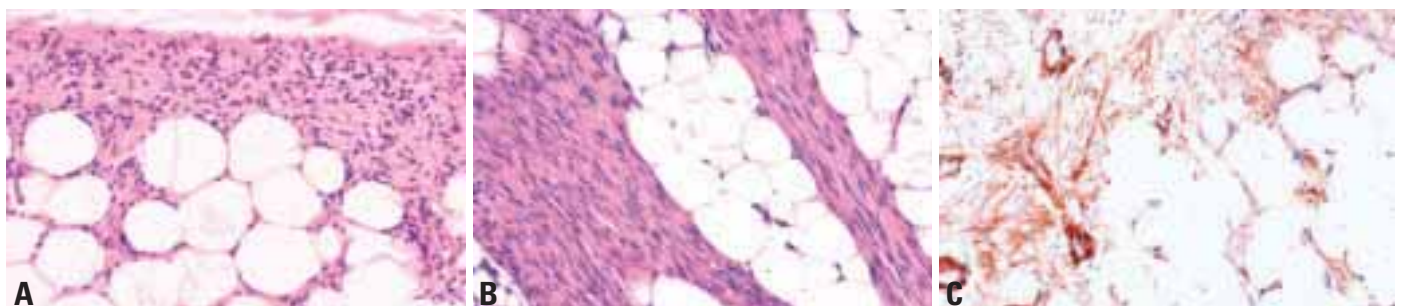


Fig. 2.58 Lipofibromatosis. **A** The spindle cell component is bland and may have a rather primitive fibroblastic appearance. **B** Fascicular growth of the fibroblastic element. **C** Focally positive immunostaining for smooth muscle actin, consistent with fibroblastic / myofibroblastic differentiation.

Extrapleural solitary fibrous tumour and haemangiopericytoma

L. Guillou
J.A. Fletcher
C.D.M. Fletcher
N. Mandahl

This section combines two neoplastic entities, the border between which has become increasingly blurred. In particular, the delineation of haemangiopericytoma as a separate entity may become obsolete since its histopathological features, as generally understood at the present time, are shared by a variety of soft tissue tumours.

Solitary fibrous tumour

Definition

A ubiquitous mesenchymal tumour of probable fibroblastic type which shows a prominent haemangiopericytoma-like branching vascular pattern. Morphologically, extrapleural solitary fibrous tumours (SFT) resemble pleural SFTs; most were termed haemangiopericytomas in the past.

ICD-O code

Solitary fibrous tumour 8815/1

Epidemiology

Extrapleural SFTs are uncommon mesenchymal neoplasms of ubiquitous location, observed in middle-aged adults between 20 and 70 years (median: 50 years), with no sex predilection. Occasional cases occur in children and adolescents.

Sites of involvement

SFTs may be found at any location. 40% of tumours are found in the subcuta-

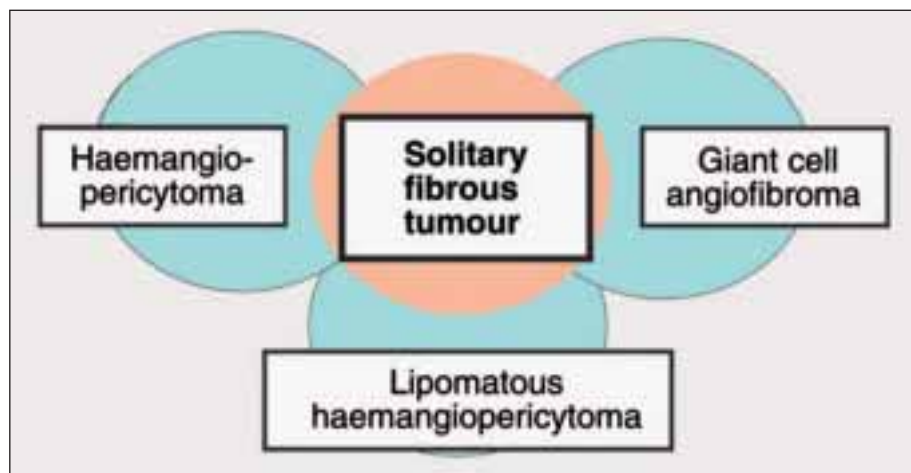


Fig. 2.59 Extrapleural solitary fibrous tumour and related lesions.

neous tissue, others are found in the deep soft tissues of extremities or extra-compartmentally in the head and neck region (especially the orbit), thoracic wall, mediastinum, pericardium, retroperitoneum, and abdominal cavity. Other described locations include the meninges, spinal cord, periosteum as well as organs such as the salivary glands, lungs, thyroid, liver, gastro-intestinal tract, adrenals, urinary bladder, prostate, spermatic cord, testes, etc. [27,283,895,896,1406,1561,2062,2073,2254].

Clinical features

Most tumours present as well delineated, slowly growing, painless masses. Large

tumours may give rise to compression symptoms, especially in the nasal cavity, the orbit and the meninges. Malignant tumours are often locally infiltrative [736, 737,896,2167]. Rarely, large tumours may be the source of paraneoplastic syndromes such as hypoglycaemia due to the production of an insulin-like growth factor [545].

Macroscopy

Most SFTs present as well circumscribed, often partially encapsulated masses, measuring between 1 and 25 cm (median: 5 to 8 cm). On section, they frequently have a multinodular, whitish and firm appearance; myxoid and haemorrhagic changes are occasionally

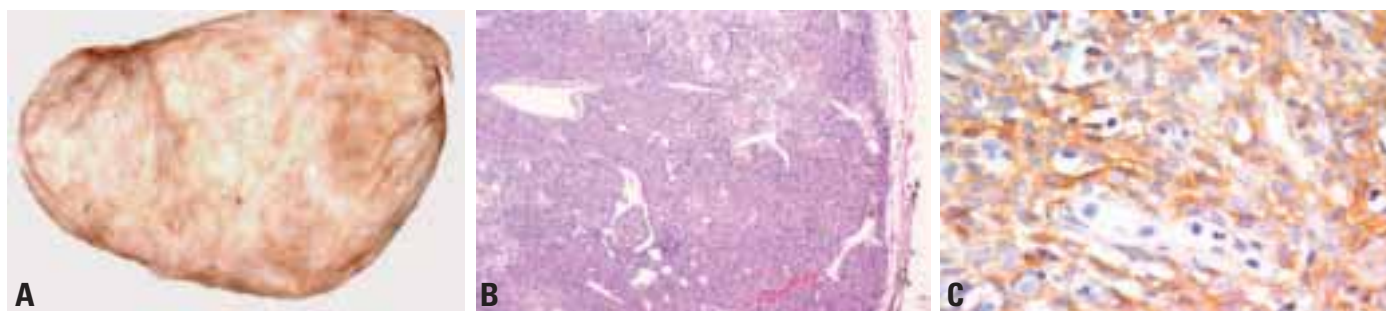


Fig. 2.60 **A** Gross appearance of an extrapleural solitary fibrous tumour. The lesion is well delineated and shows a multinodular and whitish appearance on cut section. **B** An extrapleural solitary fibrous tumour presenting as a well circumscribed but nonencapsulated mass. **C** Strong immunoreactivity of the tumour cells for CD99 in an extrapleural solitary fibrous tumour.

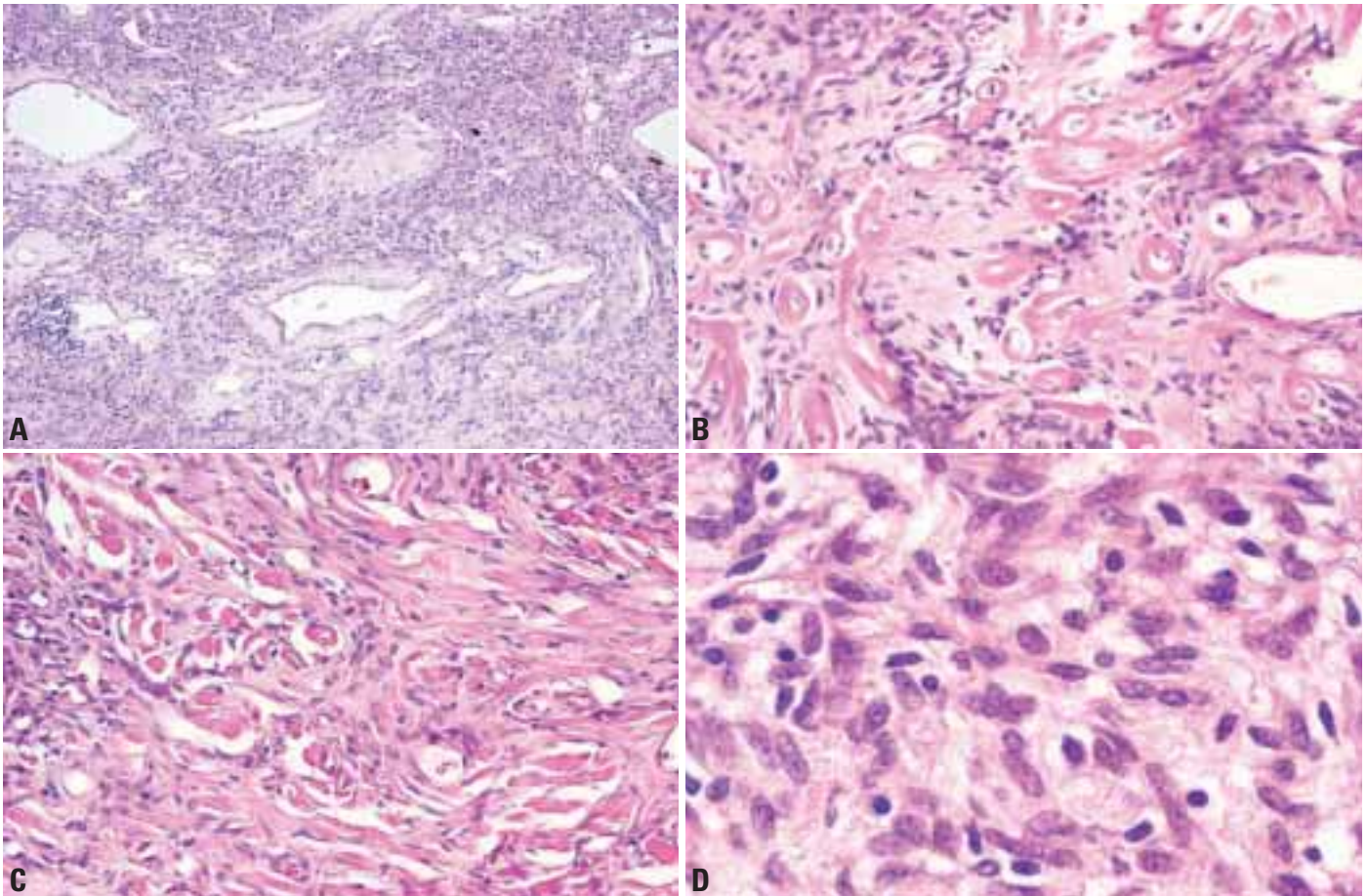


Fig. 2.61 Solitary fibrous tumour **A** Note the patternless architecture. **B** Stromal and perivascular hyalinization are common. **C** Keloidal-type collagen deposition is frequent. **D** Typically bland spindle cells with rather vesicular nuclei.

observed {736, 896, 1406, 1561, 2062, 2167}. Tumour necrosis and infiltrative margins (about 10% of cases) are mostly observed in locally aggressive or malignant tumours {737, 896, 2167}.

Histopathology

Typical SFTs show a patternless architecture characterized by a combination of alternating hypocellular and hypercellular areas separated from each other by thick bands of hyalinized, somewhat keloidal, collagen and branching haemangiopericytoma-like vessels. The non-atypical, round to spindle-shaped tumour cells have little cytoplasm with indistinct borders and dispersed chromatin within vesicular nuclei. Myxoid change, areas of fibrosis and interstitial mast cells are commonly observed. Mitoses are generally scarce, rarely exceeding 3 mitoses per 10 high-power fields. Some SFTs may contain mature adipocytes {1406, 2073} and/or giant multinucleated stromal cells {896}, overlapping morphologi-

cally with the so-called lipomatous haemangiopericytoma (see below) and giant cell angiofibroma (see above).

Malignant SFT are usually hypercellular lesions, showing at least focally moderate to marked cytological atypia, tumour necrosis, numerous mitoses (≥ 4 mitoses per ten high-power fields) and/or infiltrative margins {737, 896, 2167}. Rare cases show abrupt transition from conventional benign-appearing SFT to high grade sarcoma, likely representing a form of dedifferentiation.

Immunophenotype

Tumour cells in SFT are characteristically immunoreactive for CD34 (90 to 95% of cases) {283, 896, 1406, 1561, 2062, 2167, 2254}, and CD99 (70%) {1783}. 20 to 35% of them are also variably positive for epithelial membrane antigen, BCL2 {343, 2060}, and smooth muscle actin. Focal and limited reactivity for S100 protein, cytokeratins and/or desmin has also occasionally been reported {736, 2167}.

Ultrastructure

Ultrastructural features are nonspecific in SFT. Tumour cells often demonstrate features of fibroblastic, myofibroblastic and/or (arguably) pericytic differentiation {1406, 1556, 2073}.

Genetics

SFTs are cytogenetically heterogeneous {441, 682}. Demonstrable cytogenetic aberrations are particularly uncommon in smaller SFTs, but are found in most SFTs larger than 10 cm in diameter {1452}.

Prognostic factors

Although most cases are benign, the behaviour of SFT is unpredictable. Roughly, 10 to 15% behave aggressively, thus long-term follow-up is mandatory {736, 896, 2167}. There is no strict correlation between morphology and behaviour. However, most (but not all) histologically benign SFTs prove to be non-recurring and non-metastasizing lesions, and most histologically malignant tumours behave

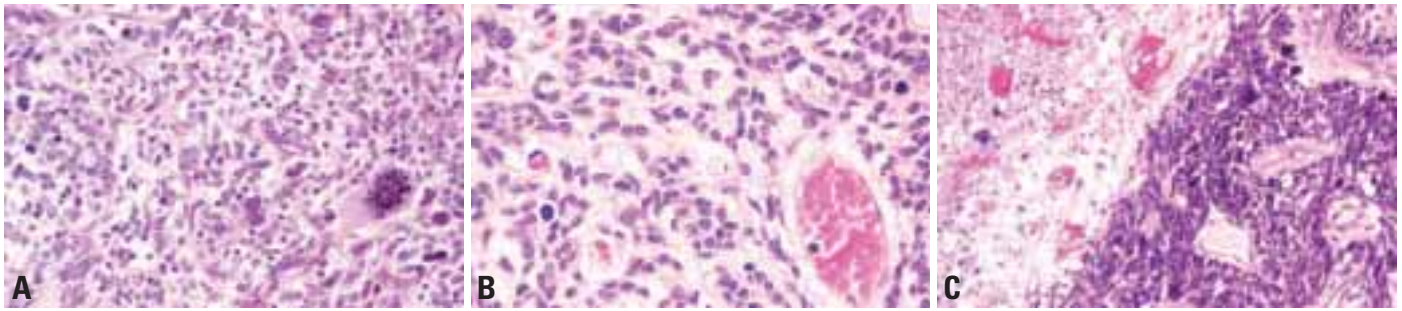


Fig. 2.62 Malignant extrapleural solitary fibrous tumours. **A** Hypercellularity and marked cytological atypia. Note the atypical mitosis. **B** Moderately cellular area with brisk mitotic activity. **C** Hypercellularity, marked cytological atypia, and areas of tumour necrosis (left).

aggressively. Lesions located in the mediastinum, abdomen, pelvis, and/or retroperitoneum also tend to behave more aggressively than those in the limbs {736,737,896,2167}. Metastases are most frequently observed in lungs, bone and liver {2167}.

Haemangiopericytoma

Definition

The residual group of lesions, previously combined under the term haemangiopericytoma, which closely resemble cellular areas of solitary fibrous tumour (SFT) and which appear fibroblastic in type. It has a range of clinical behaviour and is closely related to, if not synonymous with, SFT.

Historical annotation

Haemangiopericytoma (HPC), similar to malignant fibrous histiocytoma, is a term which has been used loosely to encompass a wide variety of neoplasms which have in common the presence of a thin-walled branching vascular pattern (described below) {294, 676, 1535}. As such, HPC is difficult to define at this time as a discrete entity, although lesions showing pericytic differentiation undoubtedly exist and were included in Stout's original descriptions {2036, 2040}.

The prototypical pericytic neoplasm is myopericytoma {825} (see page 138) and sinonasal HPC (see Tumours of the Upper Respiratory Tract) also appears to be pericytic in nature.

Epidemiology

The discrete subset of lesions remaining as HPC is rare. In light of the heterogeneity of lesions classified as HPC, there are no meaningful estimates of incidence. Myopericytoma appears substantially more common than the other discrete subset of lesions known as HPC which cannot currently be otherwise classified.

The discrete subset of soft tissue lesions known as HPC which currently justify retention of this nomenclature occur most often in middle-aged adults with an apparent female predominance.

Lesions formerly known as infantile HPC fall within the spectrum of infantile myofibromatosis {1412} (see respective section on page 59).

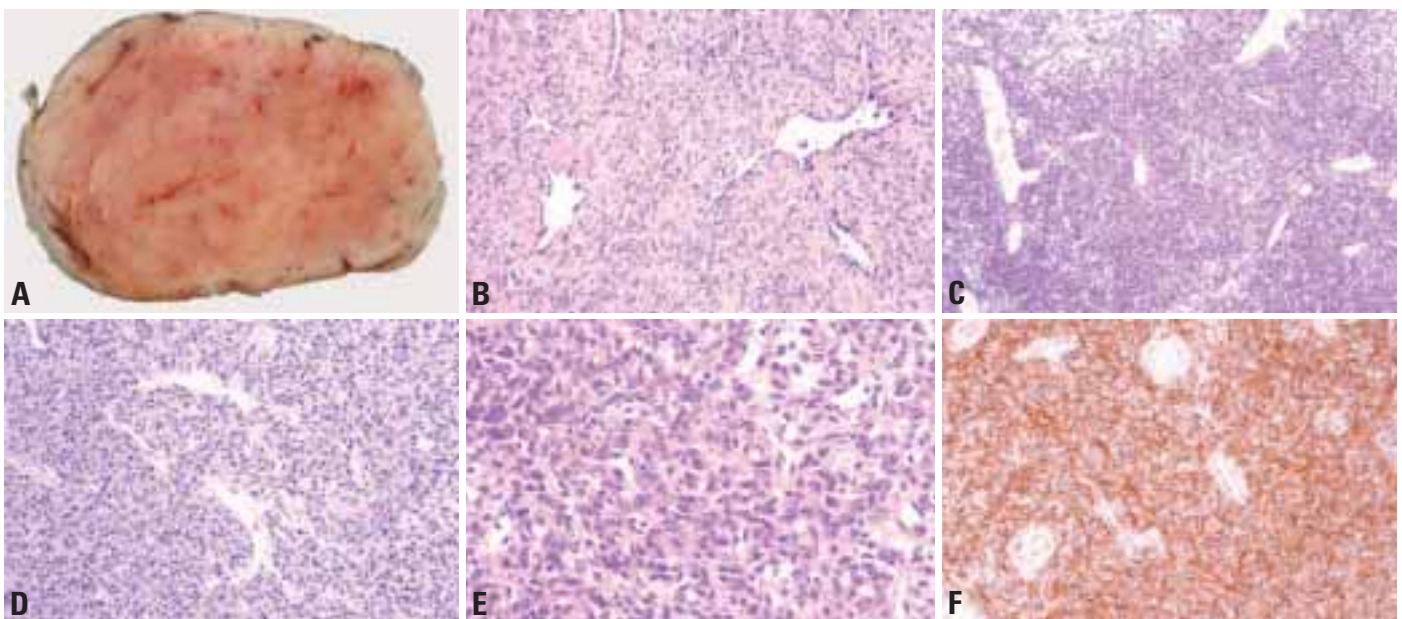


Fig. 2.63 Haemangiopericytoma. **A** This 12 cm pelvic mass was associated with hypoglycemia. Note the uniform, spongy cut surface. **B,C,D** Note the evenly distributed cellularity (in contrast to usual SFT) and the prominent branching vascular pattern. **E** Even in the more solid areas, tumour cells are arranged around numerous thin-walled vessels. Tumour cells are small with monomorphic nuclei and eosinophilic cytoplasm. **F** Diffuse positivity for CD34 is shared by the spectrum of lesions known as haemangiopericytoma and solitary fibrous tumour.

Sites of involvement

The subset of soft tissue lesions which, for the time being, are still named HPC, arise most often in deep soft tissue, particularly pelvic retroperitoneum. A smaller proportion of cases arise in the proximal limbs or limb girdles. Histologically comparable lesions also occur in the meninges (see WHO Blue Book on Tumours of the Nervous System).

Clinical features

Most tumours present as a slowly growing mass which, in the abdomen, may cause intestinal or urinary symptoms. Occasional cases, similar to SFT, are associated with hypoglycemia due to secretion of insulin-like growth factor [1671].

Macroscopy

Convincing examples of so-called HPC in soft tissue tend to be well-circumscribed masses with a yellowish or tan cut surface and a fleshy or spongy consistency. Large vessels may be evident on the cut surface. Haemorrhage is common but necrosis is infrequent. Tumour size is variable but most cases are 5-15 cm in maximum diameter.

Histopathology

The discrete residual subset of so-called HPC closely resembles the cellular areas of SFT, albeit with the consistent presence of numerous, variably ectatic or compressed, thin-walled branching vessels often having a staghorn configuration. Tumour cells are usually closely packed, spindle-shaped to round, of uniform size, with small amounts of pale or eosinophilic cytoplasm with indistinct margins and small, bland often vesicular nuclei. Cytological pleomorphism is generally not a feature. In contrast to SFT, stromal hyalinization and varying cellularity are not usual features. The mitotic rate is highly variable. Some cases contain a prominent adipocytic component (such cases are known as lipomatous HPC – see below). These lesions also often show varying cellularity and are increasingly regarded as a variant of SFT. Tumours which very often were classified as HPC in the past include (among others) solitary fibrous tumour (p. 86), monophasic synovial sarcoma (p. 200), infantile myofibromatosis (p. 59), myopericytoma (p. 138), infantile fibrosarcoma (p. 98), deep fibrous histio-

cytoma (p. 114) and mesenchymal chondrosarcoma (p. 255).

Immunohistochemistry

The discrete subset of so-called HPC, comparable to SFT, shows fairly consistent positivity for CD34 and CD99, both of which are widely expressed in fibroblastic tumours. Endothelial markers are negative, as also (in most cases) are actin and desmin.

Ultrastructure

Most of the lesions reported as HPC have shown only undifferentiated spindle cell

or fibroblastic features. Convincing evidence of true pericytic differentiation is not seen.

Genetics

Few cytogenetically investigated HPCs, located in the lung, tongue, brain, cerebellum, soft tissues, and intrabdominally, have been reported [1477]. The vast majority of cases have had near- or pseudodiploid karyotypes with the number of aberrations ranging from one to more than 20. The chromosome aberrations are quite disparate, but breakpoints in 12q13-15 and 19q13 have been identi-

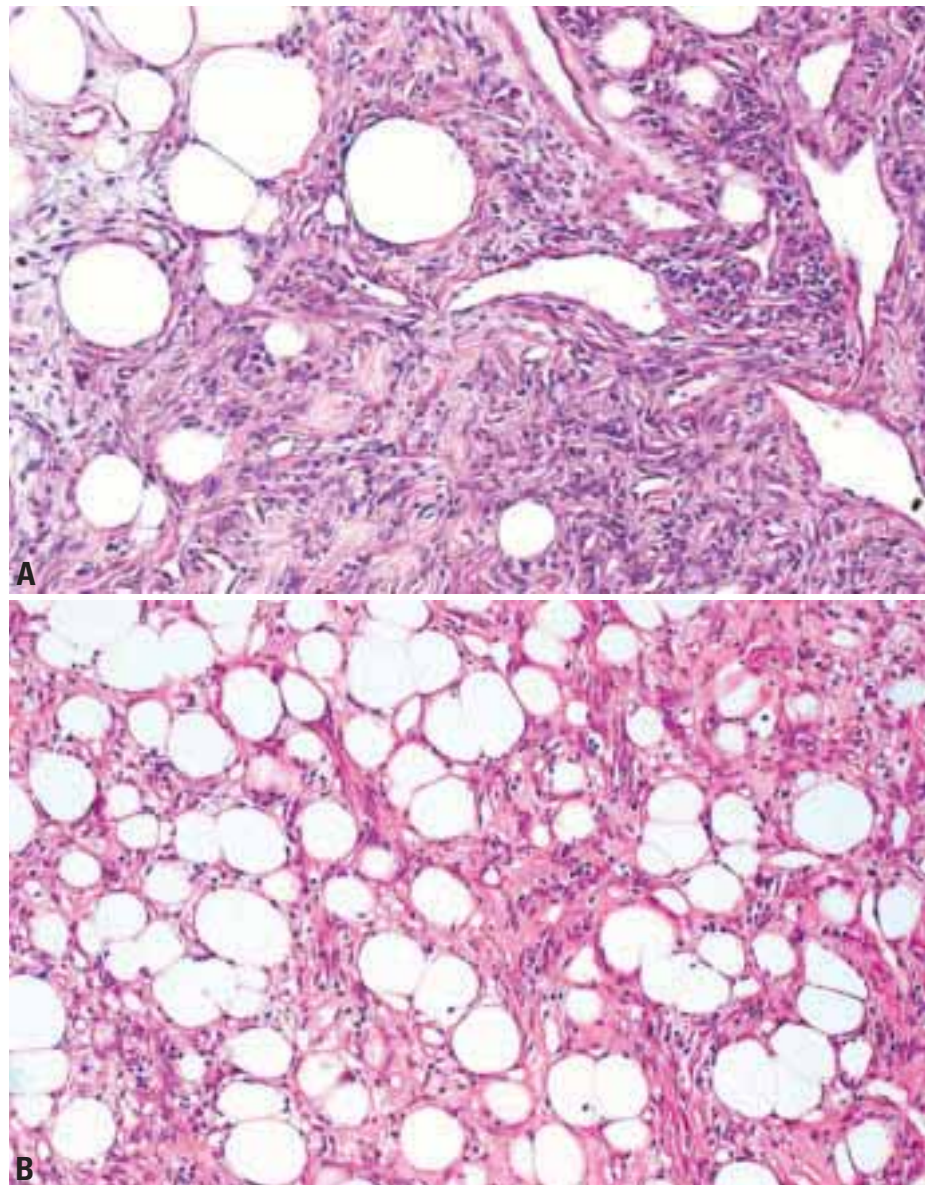


Fig. 2.64 Lipomatous haemangiopericytoma. **A** Many such lesions show features of solitary fibrous tumour in addition to containing numerous mature adipocytes. Note haemangiopericytoma-like branching vessels **B** An intimate admixture of bland spindle cells and mature adipocytes.

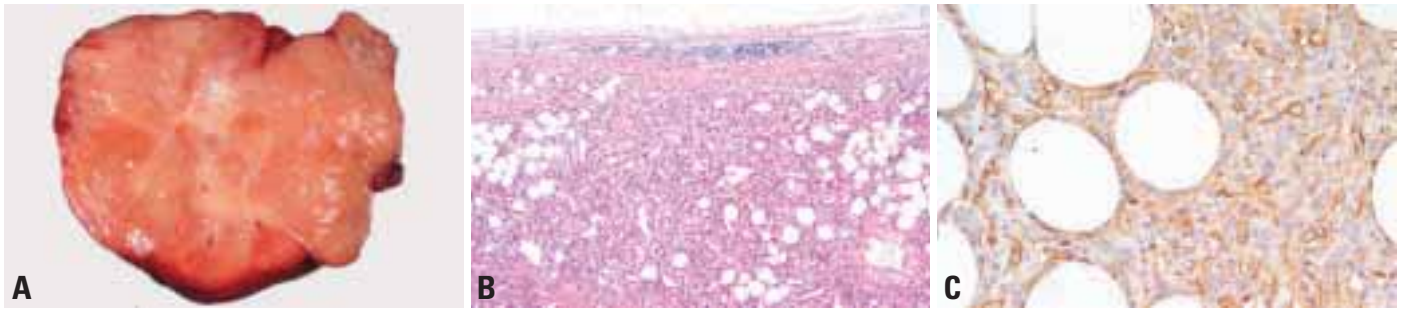


Fig. 2.65 Lipomatous hemangiopericytoma. **A** Gross appearance of a well circumscribed retroperitoneal lesion. Cut section shows fibrous bands dissecting the lesion from centre to periphery. **B** Similar to extrapleural solitary fibrous tumours, lipomatous hemangiopericytomas are well-delineated, often encapsulated masses. **C** Immunoreactivity of the tumour cells for CD34.

fied in almost half of the cases and one-fourth of the cases, respectively. In two cases, there was a balanced $t(12;19)(q13;q13)$, in one case as the sole anomaly. Among the genomic imbalances, losses are predominating. Recurrent imbalances include loss of segments in 3p, 12q, 13q, 17p, 17q, 19q, and the entire chromosome 10, and gain of 5q sequences.

Prognostic factors

At least 70% (probably more) of HPCs pursue a benign clinical course, while the remainder are malignant. Histological criteria for malignancy are imprecise and prognostication in HPC has long been regarded as difficult. There have been no recent prognostic studies confined to the

discrete subset of lesions which might nowadays be termed HPC. However, older data from major centres {598} suggest parameters similar to those used currently for SFT – specifically, 4 or more mitotic figures per 10 high power fields is the single feature most worrisome for malignancy. The presence of necrosis or nuclear pleomorphism, particularly in the context of a tumour >5 cm in diameter may also portend malignant behaviour.

Lipomatous haemangiopericytoma

Lipomatous haemangiopericytoma (LHPC) is an uncommon, slow-growing, almost non-recurring, non-metastasizing mesenchymal neoplasm composed of mature adipocytes and haemangioperi-

cytoma-like areas {696,852,1556}. LHPC shares many features with SFT. Both lesions occur in similar clinical settings, although LHPC tends to predominate in males (M/F ratio 2:1) and to affect preferentially the deep soft tissues of the lower extremity (especially the thigh) and retroperitoneum. Morphologically, it is a well demarcated neoplasm consisting of a varying combination of patternless cellular areas, prominent haemangiopericytoma-like vessels, variably collagenized extracellular matrix, and lipomatous areas made of mature adipocytes. The non atypical tumour cells are consistently positive for CD99 and, less frequently, for CD34 (75%) and BCL2 (60%) {852}.

Inflammatory myofibroblastic tumour

C.M. Coffin
J.A. Fletcher

Definition

Inflammatory myofibroblastic tumour (IMT) is a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils. It occurs primarily in soft tissue and viscera of children and young adults.

ICD-O code 8825/1

Synonyms

Plasma cell granuloma {2008,2218}, plasma cell pseudotumour {1710}, inflammatory myofibrohistiocytic proliferation {2086}, omental mesenteric myxoid hamartoma {809}, inflammatory pseudotumour {1353,1750,2151,2301}. A closely related term is inflammatory fibrosarcoma {374,1392}.

Epidemiology

IMT is primarily a visceral and soft tissue tumour of children and young adults, although the age range extends throughout adulthood. The mean age is 10 years, and the median is 9 years {376,380,960,1044,1750,2250}. Overall, IMT is most frequent in the first two decades of life. There is a slight female predominance.

Aetiology

The aetiology is unknown. The finding of human herpesvirus-8 DNA sequences and overexpression of human interleukin 6 and cyclin D1 has been recently report-

ed in 7 cases {806}. IMT has been reported following treatment for Wilms tumour {2207}.

Sites of involvement

IMT can occur throughout the body, and the most common sites are the lung, mesentery, and omentum {376,380,1701}. Among extrapulmonary IMT, 43% arose in the mesentery and omentum {380}. Other sites include soft tissue, mediastinum, gastrointestinal tract, pancreas, genitourinary tract, oral cavity,

skin, breast, nerve, bone, and central nervous system {30,203,722,960,998,1044,1071,1434,1750,1912,1999,2086,2130,2165,2209,2221,2250}.

Clinical features

The site of origin determines the symptoms of IMT. Pulmonary IMT is associated with chest pain and dyspnoea, but may be asymptomatic {1701}. Abdominal tumours may cause gastrointestinal obstruction. Dermatomyositis and obliterative phlebitis are uncommon



Fig. 2.66 Inflammatory myofibroblastic tumour presenting as a circumscribed, multinodular mass with a variegated cut surface.

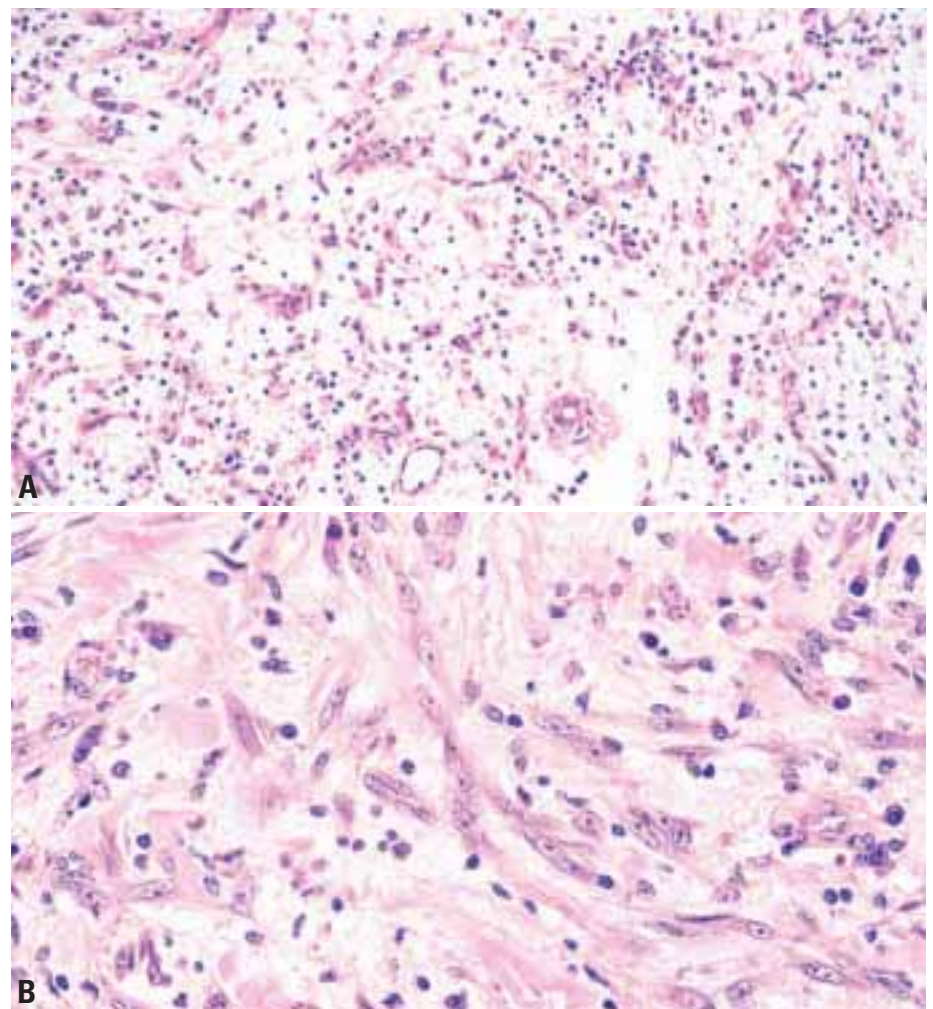


Fig. 2.67 Inflammatory myofibroblastic tumour. **A** The myxoid vascular pattern displays spindled myofibroblasts dispersed in a myxoid background with lymphocytes and plasma cells. **B** Spindled myofibroblasts and ganglion-like cells dispersed in a myxoid background with inflammatory reaction.

manifestations {26,2297}. A mass, fever, weight loss, and pain are frequent complaints. In up to one-third of patients, a clinical syndrome occurs with fever, growth failure, malaise, weight loss, anaemia, thrombocytosis, polyclonal hyperglobulinemia, and elevated erythrocyte sedimentation rate {380,1999, 2043}. When the mass is excised, the syndrome disappears, and its reappearance heralds recurrence.

Imaging studies reveal a lobulated solid mass which may be inhomogeneous {277,458}. Calcifications are sometimes detectable {1071}.

Macroscopy

The gross appearance of IMT is a circumscribed or multinodular firm, white, or tan mass with a whorled fleshy or myxoid cut surface. Focal haemorrhage, necrosis, and calcification are seen in a

minority of cases. The mean diameter of extrapulmonary IMT is 6 cm with a range of 1-17 cm {380}. In some masses, a zonal appearance with a central scar and softer red or pink periphery is seen. Multinodular tumours are usually restricted to the same anatomic region and may be contiguous or separate.

Histopathology

The spindled myofibroblasts, fibroblasts, and inflammatory cells of IMT form three basic histological patterns {376,380}. Loosely arranged plump or spindled myofibroblasts in an oedematous myxoid background with abundant blood vessels and an infiltrate of plasma cells, lymphocytes, and eosinophils resemble granulation tissue, nodular fasciitis, or other reactive processes. A second pattern is characterized by a compact fascicular spindle cell proliferation with vari-

able myxoid and collagenized regions and a distinctive inflammatory infiltrate with diffuse inflammation, small aggregates of plasma cells or lymphoid nodules. This resembles a fibromatosis, fibrous histiocytoma, or a smooth muscle neoplasm. In some instances, the spindled myofibroblastic cells surround blood vessels or bulge into vascular spaces, similar to infantile myofibromatosis or intravascular fasciitis. Ganglion-like myofibroblasts with vesicular nuclei, eosinophilic nucleoli, and abundant amphophilic cytoplasm are often seen in these two patterns. The third pattern resembles a scar or desmoid-type fibromatosis, with plate-like collagen, lower cellularity, and relatively sparse inflammation with plasma cells and eosinophils. Coarse or psammomatous calcifications and osseous metaplasia are occasionally seen {1809}.

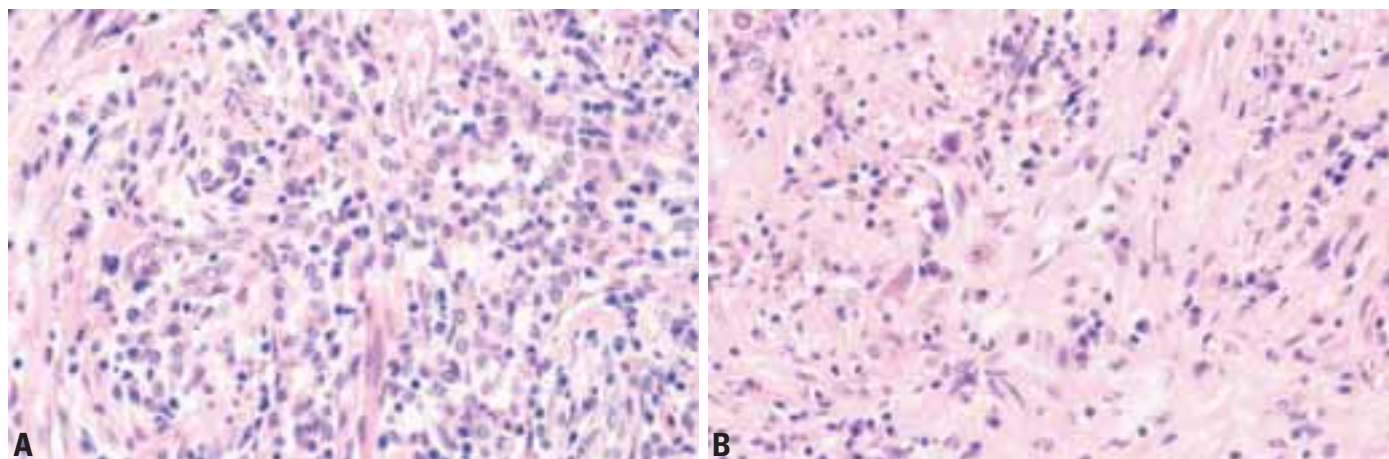


Fig. 2.68 Inflammatory myofibroblastic tumour. **A** The background contains collagen: the inflammatory infiltrate is focally dense. **B** Ganglion-like cells with vesicular nuclei and large eosinophilic nucleoli are dispersed within the fibroblastic-myofibroblastic and inflammatory proliferation.

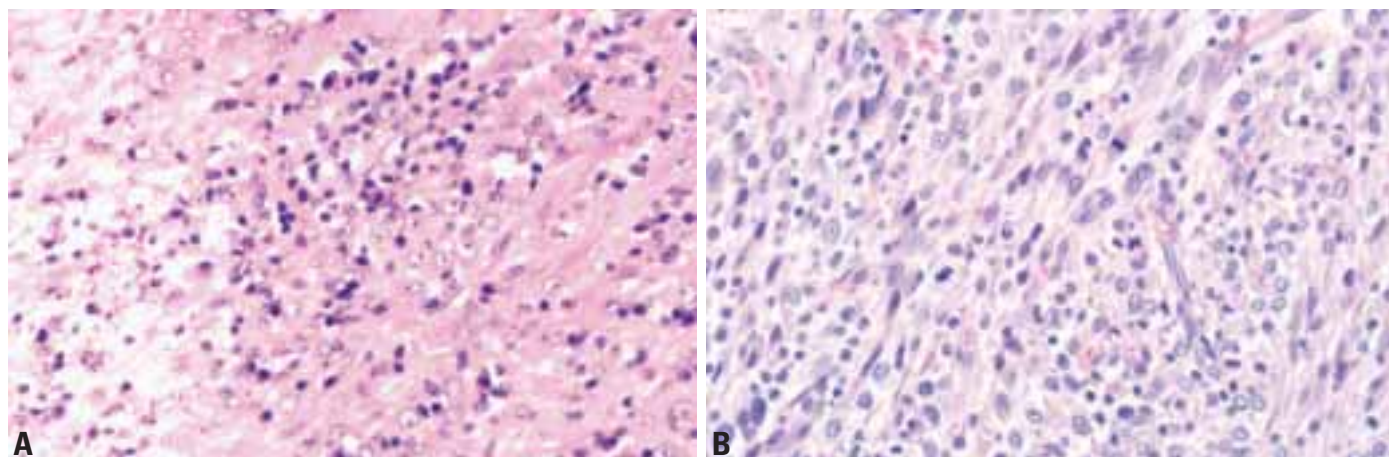


Fig. 2.69 **A** This inflammatory myofibroblastic tumour (IMT) behaved in a malignant fashion. It has large atypical vesicular nuclei and could be labelled 'inflammatory fibrosarcoma'. **B** Malignant transformation in IMT. In this example, the myofibroblasts are spindled to polygonal and show frequent mitoses and ganglion-like cells.

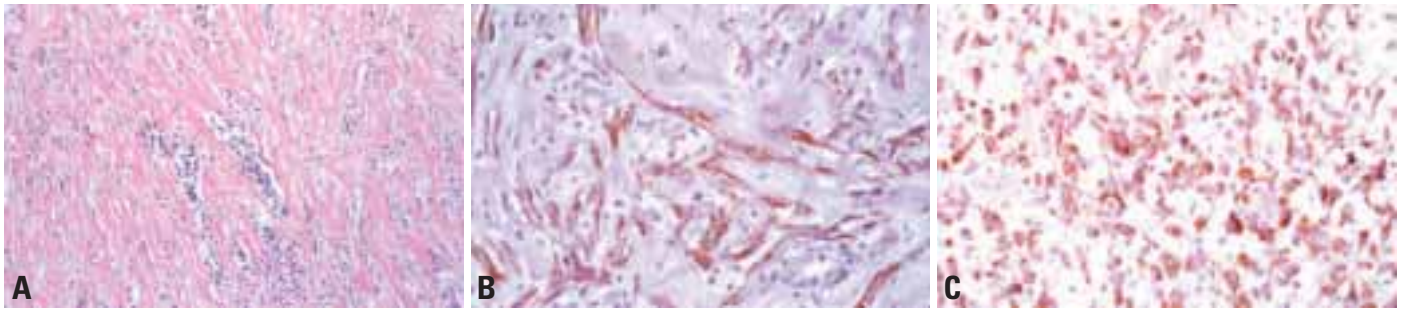


Fig. 2.70 Inflammatory myofibroblastic tumour. **A** The scar-like pattern contains abundant plate-like collagen with lower cellularity and relatively sparse inflammation. **B** Desmin is present in cytoplasm of myofibroblasts. **C** Cytoplasmic immunohistochemical reactivity for ALK (ALK1 antibody).

Highly atypical polygonal cells with oval vesicular nuclei, prominent nucleoli, and variable mitoses, including atypical forms, are seen in rare IMTs which undergo histologic malignant transformation [376,380,536]. Large ganglion-like cells and Reed-Sternberg-like cells are also seen [1475]. The round cell histiocytoid pattern may develop after multiple recurrences.

Immunophenotype

Strong diffuse cytoplasmic reactivity for vimentin is typical for virtually all IMT. Reactivity for smooth muscle actin and muscle specific actin varies from a focal to a diffuse pattern in the spindle cell cytoplasm, and desmin is identified in many cases [380,1750,2209]. Focal cytokeratin immunoreactivity is seen in about one-third of cases. Myogenin, myoglobin, and S100 protein are negative.

Immunohistochemical cytoplasmic positivity for ALK using a variety of monoclonal antibodies is detectable in approximately 50% of IMTs and correlates well with the presence of *ALK* rearrangements (occurring mainly in children) detectable by fluorescent in situ hybridization [326,378,396,838,2330]. However, ALK positivity is not specific for IMT. TP53 immunoreactivity is rare and has been reported in association with recurrence and malignant transformation [984]. IMT does not show immunoreactivity for CD117 (KIT).

Ultrastructure

IMT displays ultrastructural features of myofibroblastic and fibroblastic differentiation. Spindle cells with poorly developed Golgi, abundant rough endoplasmic reticulum, and extracellular collagen are seen, and some contain intracytoplasmic thin filaments and dense bodies [380,1392].

Genetics

IMT are heterogeneous genetically, as is hardly surprising given the varied clinicopathological entities, which have been grouped in this category. IMT in children and young adults often contain clonal cytogenetic rearrangements that activate the *ALK* receptor tyrosine kinase gene in chromosome band 2p23 [838,1226,2047]. By contrast, such rearrangements are uncommon in IMT diagnosed in adults beyond 40 years old [326,1226]. IMT with *ALK* genomic rearrangements show constitutive activation and overexpression of the ALK kinase domain, and both the *ALK* genomic rearrangements and ALK protein activation are restricted to the myofibroblastic component of the tumours [258,378,396,838,1226]. The inflammatory component is normal cytogenetically and does not express detectable ALK protein. A subset of IMT lack *ALK* oncogenic activation but contain chromosomal rearrangements targeting the *HMGIC* (also known as *HMGGA2*) gene on chromosome 12 [1080]. Notably, certain of the ALK activation

mechanisms in IMT are also found in subsets of anaplastic large cell lymphomas [1212,2125]. Immunohistochemical detection of the ALK C-terminal end is undoubtedly the most efficient method for identifying ALK oncoproteins in IMT [378,396]. The specificity of this approach is conferred by the low-to-absent expression of native ALK proteins in nonneoplastic myofibroblasts. Therefore, the finding of strong C-terminal ALK expression provides strong evidence for an oncogenic activating mechanism.

Prognostic factors

Extrapulmonary IMT has a recurrence rate of approximately 25% related to location, resectability, and multinodularity [380]. Rare cases (<5%) also metastasize. Evidence suggests that a combination of atypia, ganglion-like cells, TP53 expression, and aneuploidy may help to identify IMT with a more aggressive potential [202,203,984,1163,1750]. Unfortunately it is difficult to predict on the basis of histopathological findings alone in an individual case whether recurrence or malignant transformation will occur. Although surgery is the principal treatment, regression and response to corticosteroids and nonsteroidal inflammatory agents have been noted in rare cases [374,376,1044,2048].

Low grade myofibroblastic sarcoma

T. Mentzel
J.A. Fletcher

Definition

Low grade myofibroblastic sarcoma represents a distinct atypical myofibroblastic tumour often with fibromatosis-like features and predilection for the head and neck.

ICD-O code 8825/3

Synonym

Myofibrosarcoma.

Epidemiology

Given the lack of consensus on diagnostic criteria, myofibroblastic sarcomas in general are probably more common than currently believed, and include a variety of clinicopathological forms {1405}. Low grade myofibroblastic sarcoma represents a distinct entity that occurs predominantly in adult patients with a slight male predominance; more rarely children are affected {1414,1495,1969}.

Sites of involvement

Low grade myofibroblastic sarcoma shows a wide anatomic distribution, however, the extremities and the head and neck region, especially the tongue and the oral cavity, seem to be preferred locations {1414,1495}. Rare cases involving the salivary gland and the nasal cavity / paranasal sinus have been reported {201,1153}.

Clinical features

In most cases of low grade myofibroblastic sarcoma patients complain about a painless swelling or an enlarging mass. Pain or related symptoms have been more rarely reported. Clinically, local recurrences are common, whereas metastases only rarely occur and often after a prolonged time interval {1414}. Radiologically, these lesions have a destructive growth pattern.

Macroscopy

Grossly, most cases are described as a firm mass with pale and fibrous cut surfaces and mainly ill defined margins {1414}; a minority of neoplasms are well

circumscribed with rather pushing margins {1495}.

Histopathology

Histologically, most cases of low grade myofibroblastic sarcoma are characterized by a diffusely infiltrative growth pattern, and, in deeply located neoplasms, tumour cells may grow between individual skeletal muscle fibres. Most cases are composed of cellular fascicles or show a storiform growth pattern of spindle-shaped tumour cells. Neoplastic

cells have ill defined pale eosinophilic cytoplasm and fusiform nuclei that are either elongated and wavy with an evenly distributed chromatin, or plumper, more rounded and vesicular with indentations and small nucleoli. More rarely, hypocellular neoplasms with a more prominent collagenous matrix and focal hyalinization have been described. Importantly, neoplastic cells show at least focally moderate nuclear atypia with enlarged, hyperchromatic and irregular nuclei and a slightly increased prolifer

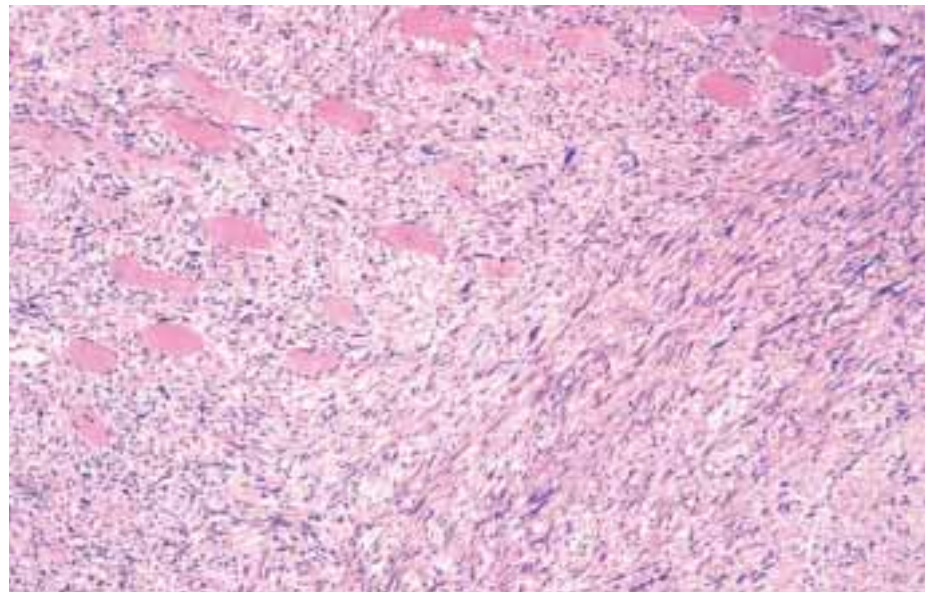


Fig. 2.71 Low grade myofibroblastic sarcoma, deep seated, presenting as a diffusely infiltrative spindle cell neoplasm with a fascicular arrangement of neoplastic cells.

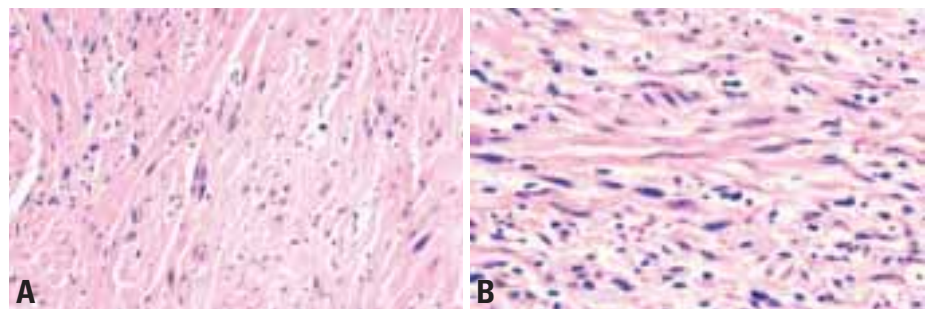


Fig. 2.72 **A** This hypocellular low grade myofibroblastic sarcoma is composed of atypical spindled neoplastic cells set in a prominent collagenous matrix. **B** Fusiform tumour cells in low grade myofibroblastic sarcoma contain ill defined, pale, eosinophilic cytoplasm and spindle-shaped nuclei that are either vesicular with small nucleoli and indentations or elongated and wavy, resembling neural differentiation.

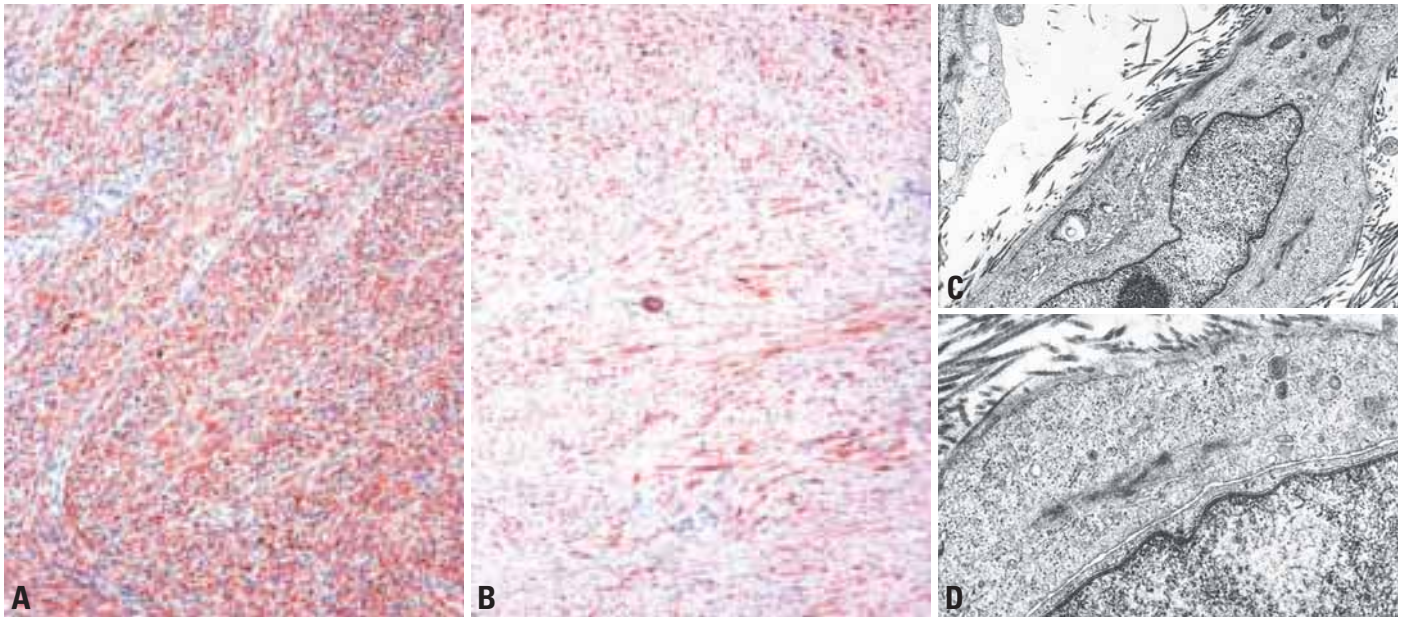


Fig. 2.73 Immunohistochemically, tumour cells in low grade myofibroblastic sarcoma often stain positively for **(A)** desmin and **(B)** for alpha-smooth muscle actin. **C, D** EM showing **(C)** a discontinuous basal lamina, **(D)** thin filaments with focal densities, subplasmalemmal attachment plaques, and micropinocytic vesicles.

erative activity. These neoplasms may contain numerous thin-walled capillaries. Lymphocytes and plasma cells are not a prominent feature.

Immunophenotype

Neoplastic cells in low grade myofibroblastic sarcoma have a variable immunophenotype: actin positive/desmin negative, actin negative/desmin positive, and actin positive/desmin positive cases. In addition, tumour cells may stain positively for fibronectin, and focal expression of CD34 and CD99 has been reported, whereas S100 protein, epithelial markers, laminin, and h-caldesmon are negative {1414}.

Ultrastructure

In contrast to smooth muscle cells, neoplastic cells in low grade myofibroblastic sarcoma contain indented and clefted nuclei, a variable amount of rough endoplasmic reticulum, and are surrounded by a discontinuous basal lamina. Unlike in fibroblasts, randomly oriented intermediate filaments and thin filaments with focal densities and subplasmalemmal attachment plaques, a discontinuous basal lamina and often micropinocytic vesicles are noted.

Genetics

Genetic aberrations have been described in only a few low grade myofi-

broblastic sarcomas. The preliminary reports are of karyotypes with a moderate number of chromosomal aberrations, substantially less complex than the karyotypes seen in most high grade myofibroblastic sarcomas {682}.

Prognostic factors

The presence of increased proliferative activity and tumour necrosis is associated with more aggressive behaviour {1495}.

Myxoinflammatory fibroblastic sarcoma

L.G. Kindblom
J.M. Meis-Kindblom

Definition

Myxoinflammatory fibroblastic sarcoma (MIFS) is a unique low grade sarcoma with myxoid stroma, inflammatory infiltrate and virocyte-like cells that predominantly involves the hands and feet.

ICD-O code 8811/3

Synonyms

Inflammatory myxohyaline tumour of the distal extremities with virocyte or Reed-Sternberg-like cells {1496}, acral myxoinflammatory fibroblastic sarcoma, inflammatory myxoid tumour of the soft parts with bizarre giant cells {1437}.

Epidemiology and aetiology

MIFS is rare and occurs primarily in adults with a peak incidence in the fourth and fifth decades. Males and females are equally affected.

The prominent acute and chronic inflammation seen in this lesion, presence of inclusion-like nucleoli in tumour cells, and history of a longstanding mass in many patients raise the possibility of an infectious aetiology. However, no evidence of CMV or EBV has been detected in MIFS using immunohistochemical and PCR techniques {1496}, and stains for bacteria, fungi and mycobacteria have been uniformly negative {1386}.

Clinical features

Two large series of this entity, including 44 and 51 cases, indicate a predilection for the distal extremities {1386,1496}. Two-thirds of tumours involve the hands and wrists and one-third the feet and ankles. The elbows and knees are rarely involved. Most patients have a relatively long history of a slowly growing, poorly defined mass that is occasionally associated with pain and decreased mobility. The preoperative diagnosis in most cases is benign and may include tenosynovitis, ganglion cyst, and giant cell tumour of tendon sheath.

Macroscopy

Most lesions are poorly defined and

multinodular and frequently have alternating fibrous and myxoid zones. Tumour size ranges from less than 1 to 8 cm; median tumour size is 3–4 cm.

Morphology

The tumours typically infiltrate the subcutaneous fat and frequently involve the joints and tendons. Dermal invasion is often seen, whereas invasion of skeletal muscle is rare. Bone involvement has not been observed.

The most striking feature at low magnification is a prominent dense, mixed acute and chronic inflammatory infiltrate associated with alternating hyaline and myxoid zones in variable proportions. Aggregates of macrophages and uniform mononuclear cells with foci of haemosiderin deposition closely resemble pigmented villonodular synovitis. There are three main types of neoplastic cells seen in MIFS, including spindled cells, large polygonal and bizarre ganglion-like cells with huge inclusion-like nucleoli, and variably sized bubbly, multivacuolated lipoblast-like cells. These cells may be scattered singly or form coherent nodules.

Immunophenotype

The neoplastic cells are strongly positive for vimentin, variably positive for CD68 and CD34, and rarely positive for smooth muscle actin {1386}. Occasional cases show weak cytokeratin positivity. More importantly, they are negative for leukocyte common antigen, T and B-cell markers and CD30.

Ultrastructure

All three types of neoplastic cell display features of fibroblasts, including abundant rough endoplasmic reticulum and mitochondria, and a network of intermediate filaments occasionally forming densely packed perinuclear whorls {1386}.

The tumour cells simulating lipoblasts demonstrate cytoplasmic pseudoinclusions containing extracellular mucinous material.

Genetics

The only case for which cytogenetic information exists showed a t(1;10) together with loss of chromosomes 3 and 13 {1213}.

Prognostic factors

Reported rates of local recurrence vary widely, ranging from 20% to 70% {1386, 1496}. In one large series, repeated local recurrences with proximal extension eventually culminated in amputation in more than one-third of patients who had local recurrences {1386}. Differences in reported rates of local recurrence may be attributed to differences in primary surgical treatment, a high rate of misdiagnosis as a benign tumour, and differences in length of clinical follow-up.

Metastases to distant lymph nodes and lung occur but are exceedingly rare (<2% of all reported cases), based on currently available data {1386}.



Fig. 2.74 T1-weighted MRI with contrast enhancement, showing an MIFS involving the dorsal foot.

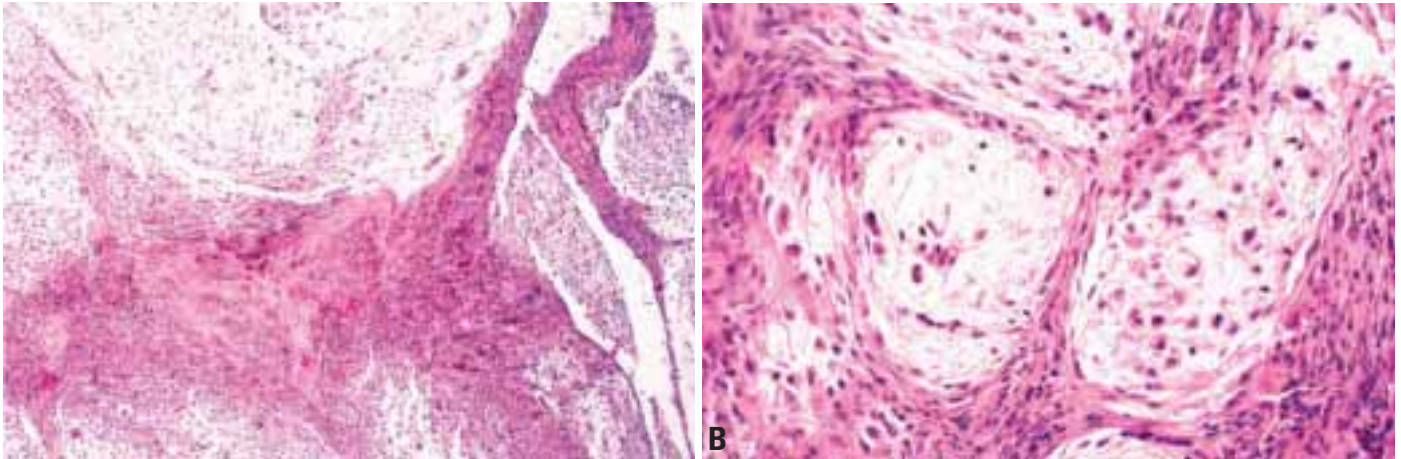


Fig. 2.75 Myxoinflammatory fibroblastic sarcoma (MIFS). **A, B** Note the alternating areas of myxoid tissue and more solidly cellular tissue containing inflammatory cells.

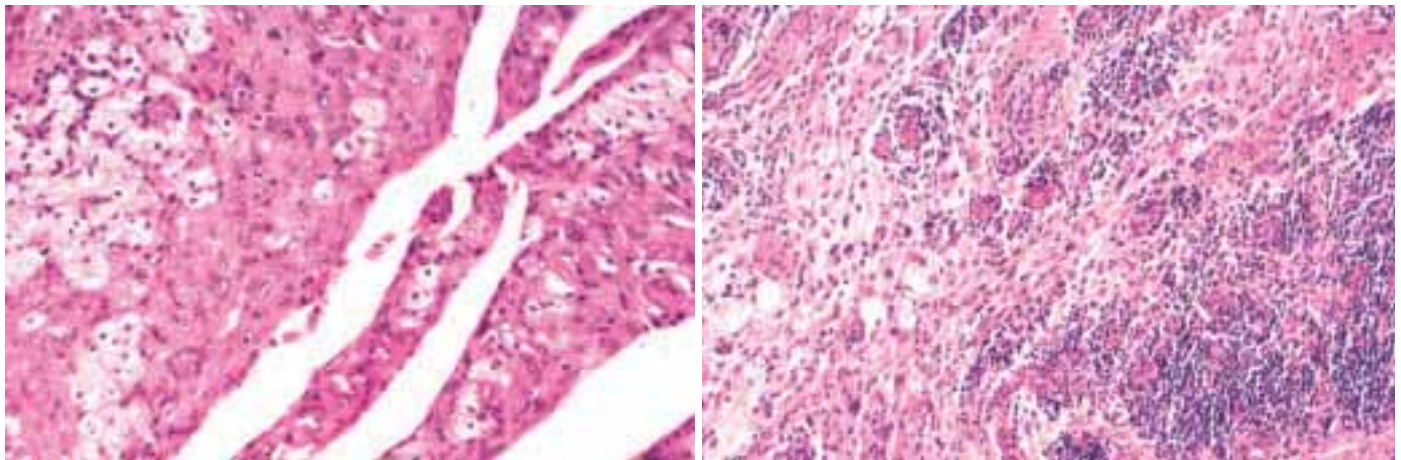


Fig. 2.76 Myxoinflammatory fibroblastic sarcoma (MIFS). Clusters of **(A)** macrophages and **(B)** lymphocytes may obscure the tumour cells.

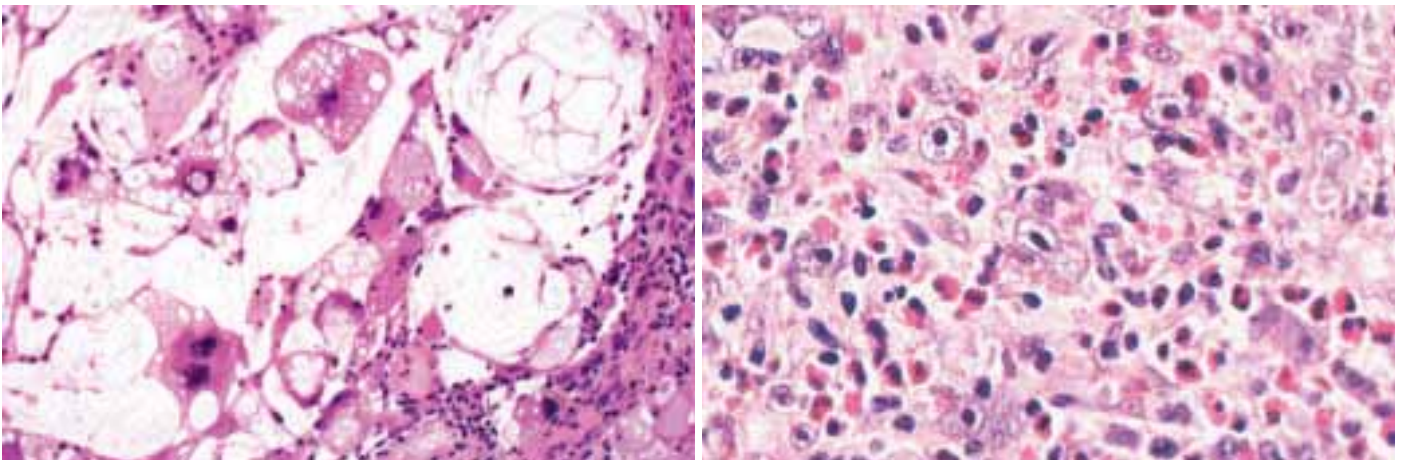


Fig. 2.77 Myxoinflammatory fibroblastic sarcoma (MIFS). **A** Confluent myxoid nodules containing pleomorphic, bizarre, lipoblast-like cells. **B** Large polygonal fibroblasts with inclusion-like nucleoli. Note the presence of prominent eosinophils.

Infantile fibrosarcoma

C.M. Coffin
J.A. Fletcher

Definition

Infantile fibrosarcoma (IFS) is histologically identical to classic fibrosarcoma of adults, but carries a much more favourable prognosis. It occurs in infants and young children, metastasizes rarely, and has a natural history similar to that of fibromatoses. IFS is morphologically and genetically related to congenital mesoblastic nephroma.

ICD-O code 8814/3

Synonyms

Congenital fibrosarcoma {214}, congenital-infantile fibrosarcoma {377}, juvenile fibrosarcoma {2038}, medullary fibromatosis of infancy, aggressive infantile fibromatosis, congenital fibrosarcoma-like fibromatosis, desmoplastic fibrosarcoma of infancy, medullary fibromatosis of infancy {40,1924}.

Epidemiology

IFS accounts for approximately 13% of fibroblastic-myofibroblastic tumours in children and adolescents {372} and 12% of soft tissue malignancies in infants {888}. 36%-80% of cases are congenital, and 36%-100% of cases occur in the first year of life {350,377,1017,1848,2001,2038}. IFS is seldom encountered after 2 years of age {377} and in that context would require cytogenetic confirmation. There is a slight male predominance.

Aetiology

The aetiology is unknown. No definite predisposing factors, associated heredi-

tary diseases, or causative agents have been demonstrated. Prenatal radiation, multiple congenital anomalies, congenital naevus, meningomyelocele, and Gardner syndrome have been reported in sporadic cases {377,628,847,915}.

Sites of involvement

The superficial and deep soft tissues of the extremities, especially distally, are the most common sites, accounting for 61% of cases overall {117,214,350,377}. The trunk (19% of cases) and head and neck (16%) are other major sites. The mesentery and retroperitoneum are rarer sites of origin.

Clinical features

IFS presents as a solitary enlarging, nontender mass or swelling in the soft tissues and grows rapidly {350,377,915,2038}. The diameter may exceed 30 cm {377}. Congenital and infantile cases are often grotesquely large in proportion to the size of the child. The overlying skin is tense, erythematous, and ulcerated. Imaging studies reveal a large soft tissue mass with a heterogeneous enhancement pattern and variable osseous erosion {117,214,572}.

Macroscopy

IFS is a poorly circumscribed, lobulated mass that infiltrates adjacent soft tissue. Compression of adjacent tissue gives the appearance of a pseudocapsule, but the actual margins are irregular and infiltrative. The cut surface is soft to firm,

fleshy, and grey to tan with variable areas of myxoid or mucinous change, cystic degeneration, haemorrhage, necrosis, and yellow-red discoloration {117,350,424,1808,2035,2038}.

Histopathology

The typical IFS is a densely cellular neoplasm composed of intersecting fascicles of primitive ovoid and spindle cells with a herringbone pattern or forming interlacing cords, sinuous bands or sheets of cells. Zonal necrosis and haemorrhage are frequent and may be associated with dystrophic calcifications {350,377,424,2038}. The cells show little pleomorphism. Giant cells are not usually seen. Collagen formation is variable, and mitotic activity is prominent. Most IFS contain scattered chronic inflammatory cells and may display focal extramedullary haematopoiesis. Histological variations include a focally prominent haemangiopericytoma-like pattern of irregular cavernous or clefted blood vessels, dilated blood vessels with fibrin thrombi, myxoid foci, or a predominant round or ovoid immature cellular proliferation with minimal collagen. Infiltrative growth results in entrapment of adipose tissue, skeletal muscle and other structures. Rarely, recurrent IFS displays features resembling a high grade pleomorphic sarcoma {1848}. Composite tumours with overlapping features of infantile myofibromatosis, infantile haemangiopericytoma, and infantile fibrosarcoma are occasionally encountered {2194}.

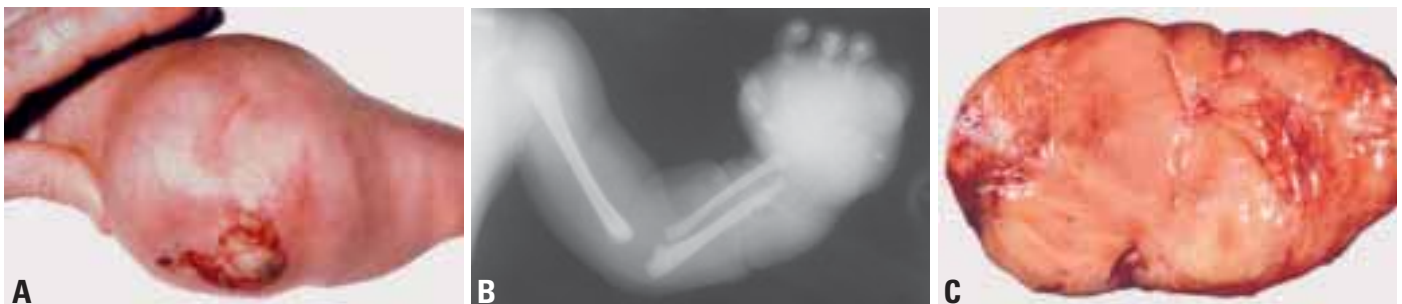


Fig. 2.78 Infantile fibrosarcoma (IFS). **A** IFS of the knee presenting as a large mass with purple discoloration and focal cutaneous ulceration. **B** X-ray of an large IFS of the hand. **C** IFS in soft tissue, displaying a fleshy, tan-white cut surface with focal haemorrhage, necrosis, and myxoid change.

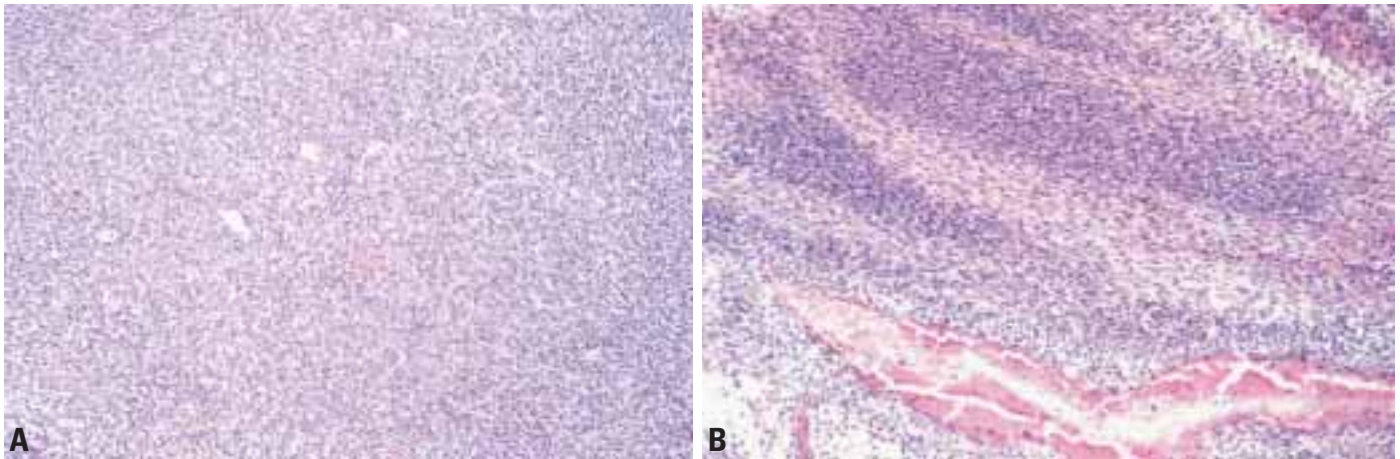


Fig. 2.79 Infantile fibrosarcoma. **A** Poorly formed fascicular growth pattern. **B** A herringbone pattern is present with variable collagen deposition.

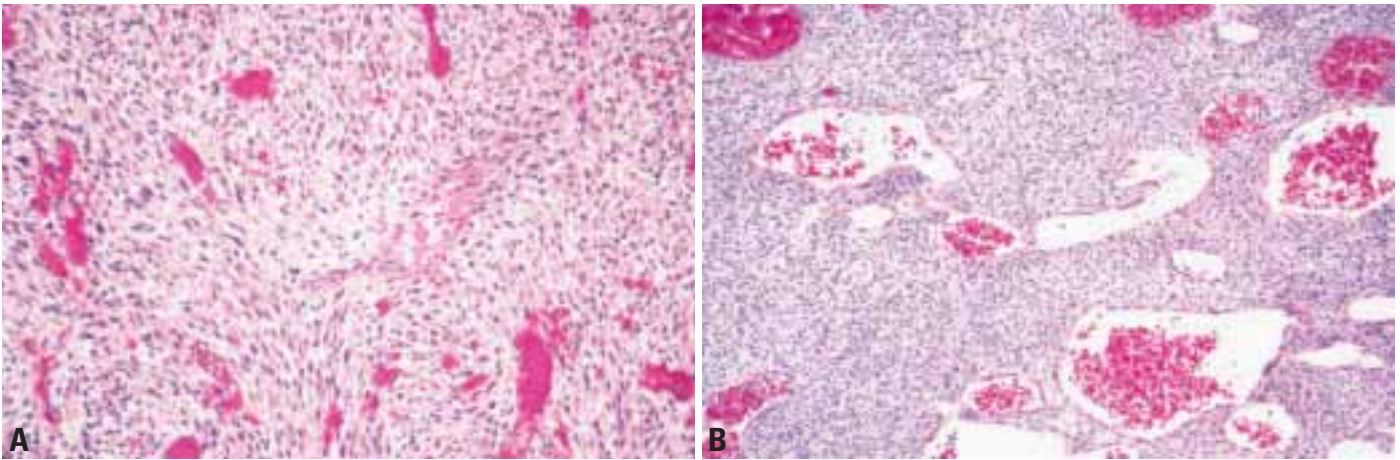


Fig. 2.80 Infantile fibrosarcoma. **A** Short interlacing fascicles, congested blood vessels, and zonal necrosis. **B** Dilated, irregularly branching blood vessels in IFS simulate haemangiopericytoma.

Immunophenotype

The immunohistochemical features of IFS have been reported by several groups with somewhat non-specific findings {377,1151,1933,2194,2278}. Vimentin immunoreactivity is found in 100%, but otherwise IFS is heterogeneous for markers such as neuron-specific enolase (35%), alpha-smooth muscle actin (33%), HHF35 actin (29%), and muscle-specific actin (30%). Fewer than 20% of cases are positive for desmin, S100 protein, CD34, CD57, CD68, factor XIIIa, and CAM5.2 cyokeratin.

Ultrastructure

IFS displays electron microscopic characteristics of fibroblasts and myofibroblasts, with a variable histiocytic component {82,424,807,810}. The cells have large nuclei, one or more nucleoli, dilated

rough endoplasmic reticulum with dense material, variably abundant lysosomes, focal basement membrane-like material, and cytoplasmic filaments. In some cases, bundles of thin filaments are seen {1151}.

Genetics

Most infantile fibrosarcomas contain a chromosomal translocation $t(12;15)(p13;q26)$ involving exchange of material between 12p and 15q, resulting in oncogenic activation of the *NTRK3* (a.k.a. *TRKC*) receptor tyrosine kinase gene {235,1142}. The mechanism of activation is a fusion of the 12p *ETV6* (a.k.a. *TEL*) gene to the 15q *NTRK3* gene, and the associated oncoprotein contains the N-terminal aspect of *ETV6* fused to the *NTRK3* kinase domain. The *ETV6/NTRK3* fusion mechanism is cytogenetically sub-

tle, when assessed by conventional chromosome banding methods {1142,1816}. However, *ETV6/NTRK3* rearrangement can be demonstrated readily by molecular cytogenetic methods or RT-PCR {16,80,235,553,1142,1816}. Trisomies for chromosomes 8, 11, 17 and 20 are nearly as characteristic as the *ETV6/NTRK3* fusion in infantile fibrosarcomas {1892}. These trisomies appear to be acquired after the *ETV6/NTRK3* fusion, and are perhaps responsible for inducing progression to a more mitotically-active neoplasm {1816}. Notably, a genetic profile similar to that in infantile fibrosarcoma is also seen in mixed-histology and cellular congenital mesoblastic nephroma. Therefore, the pathogenesis of congenital fibrosarcoma and congenital mesoblastic nephroma are doubtless closely related {1141,1816,1893}.

Prognostic factors

IFS has a favourable outcome when compared with adult fibrosarcoma. The mortality ranges from 4% to 25%, and the recurrence rate is 5% to 50% {350,377, 1017,1848,2001,2038}. Metastasis is rare in more recent series {350,377,2001}. No definitive morphological or genetic prognostic factors have been identified. Haemorrhage and involvement of vital structures by locally aggressive tumours may cause death {377}. Spontaneous regression and nonrecurrence of incompletely excised IFS have been reported {530,1101,1305,1708,2009,2278}. Although surgery is the mainstay of treatment, chemotherapy has been proven effective {371,1185,1195,1797,1938}.

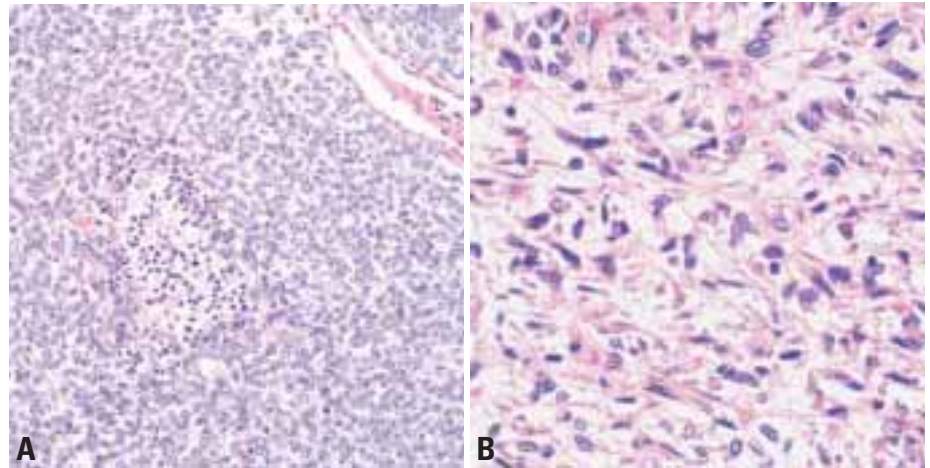


Fig. 2.81 Infantile fibrosarcoma (IFS). **A** A round cell pattern is a variant of IFS. **B** A myxoid focus in IFS contains primitive spindle and ovoid cells.

Adult fibrosarcoma

Definition

Adult fibrosarcoma is a malignant tumour, composed of fibroblasts with variable collagen production and, in classical cases, a herringbone architecture. It is distinguished from infantile fibrosarcoma and from other specific types of fibroblastic sarcomas.

ICD-O code 8810/3

Epidemiology

The incidence of this tumour is difficult to assess because its diagnosis is partly one of exclusion, and because in recent years specific subtypes of fibrosarcoma (see page 47) have been defined. At most, it probably accounts for 1 to 3% of adult sarcomas {667}. Mixed patterns occur. Classical fibrosarcoma is most common in middle-aged and older adults, but an occasional tumour of this type is seen in childhood (see also section on infantile fibrosarcoma). The sex incidence is equal.

Sites of involvement

Fibrosarcomas involve deep soft tissues of extremities, trunk, head and neck. Fibrosarcoma has also been reported in visceral organs but the identity of these in older reports is questionable. Retroperitoneal fibrosarcoma is rare.

Clinical features

Fibrosarcoma presents as a mass with or without pain. In specific sites local symptoms relate to the effects of a mass. Hypoglycemia has been reported.

Aetiology

There are no specific predisposing factors. Some arise in the field of previous therapeutic irradiation, and rarely in association with implanted foreign material {6}, although the nature of these tumours in the older literature is not always certain. Tumours with the histological features of adult fibrosarcoma may arise in dermatofibrosarcoma (see WHO Tumours of Skin), solitary fibrous

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tumour (see page 86) and in well differentiated liposarcoma (see page 35), either in the primary or in recurrence, as a reflection of tumour progression.

Macroscopy

The typical fibrosarcoma is a circumscribed white or tan mass, variably firm in relation to the collagen content. Haemorrhage and necrosis can be seen in high grade tumours

Histopathology

The tumour is composed of spindle-shaped cells, characteristically arranged in sweeping fascicles that are angled in a chevron-like or herringbone pattern {2035}. Storiform areas can be seen. The cells have tapered darkly staining nuclei with variably prominent nucleoli and scanty cytoplasm. Mitotic activity is almost always present but variable. Higher grade tumours have more densely staining nuclei, and can display focal round cell change and multinucleated

cells, but sarcomas with significant pleomorphism are classified as so-called malignant fibrous histiocytomas (undifferentiated pleomorphic sarcoma). The stroma has variable collagen, from a delicate intercellular network to paucicellular areas with diffuse or "keloid-like" sclerosis or hyalinization. Myxoid change and osteochondroid metaplasia can occur. Fibrosarcoma is usually more cellular than fibromatosis and has larger more hyperchromatic nuclei. However, fibromatosis-like areas can be seen in fibrosarcoma so that tumours should be carefully sampled.

Immunophenotype

Fibrosarcomas are positive for vimentin and very focally for smooth muscle actin, representing myofibroblastic differentiation. Some cases arising in dermatofibrosarcoma or solitary fibrous tumour are CD34 positive.

Ultrastructure

Fibrosarcoma is composed of fibroblasts with prominent rough endoplasmic reticulum and absence of myofilaments, external lamina or intercellular junctions. An occasional cell has peripheral filament bundles suggestive of myofibroblastic differentiation but tumours in which this is a prominent feature should be classified as myofibrosarcomas.

Genetics

Adult fibrosarcoma shows multiple chromosome rearrangements of a complex nature without characteristic anomalies

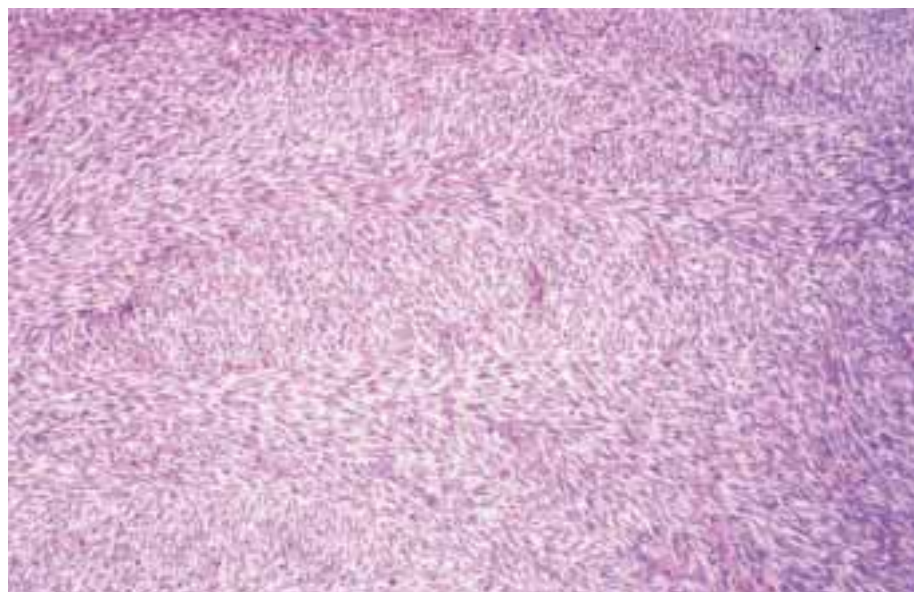


Fig. 2.82 Adult fibrosarcoma. Low power view shows the classical adult-type lesion with a herringbone growth pattern.

{436,1263,1477,2173}. However, two cases of adult fibrosarcoma showed involvement of the same 2q21-qter segment, leading to partial tri- or tetrasomy for 2q {1263}. Based on this finding and other reported cases, disruption of one or more genes in the 2q14-22 region might contribute to the pathogenesis of some adult fibrosarcomas.

Prognostic factors

There are no recent series of fibrosarcoma, which have utilised current definitions. In the older literature, for tumours regarded as fibrosarcoma, behaviour is

related to grade and to general factors of tumour size and depth from surface. The probability of local recurrence relates to completeness of excision, with recurrence rates of 12-79% {1730,1731,1914}.

Fibrosarcomas metastasize to lungs and bone, especially the axial skeleton, and rarely to lymph nodes. Metastasis occurs in 9-63% of patients and is time- and grade-dependent. 5 year survival is 39-54% {1731,1914}. Poor prognostic factors include high grade, high cellularity with minimal collagen, mitotic rates >20/10 hpf, necrosis, and little collagen.

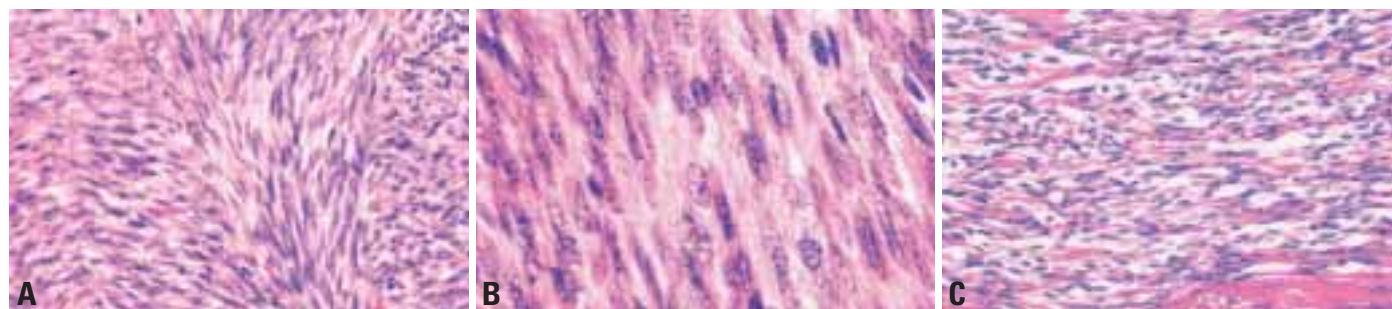


Fig. 2.83 Adult fibrosarcoma. **A** Cells are arranged in long intersecting fascicles with a herringbone pattern. **B** Short tapered spindle cells with scanty cytoplasm and mildly pleomorphic nuclei. **C** Tumour cells are separated by delicate intercellular collagen fibres.

Myxofibrosarcoma

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Definition

Myxofibrosarcoma comprises a spectrum of malignant fibroblastic lesions with variably myxoid stroma, pleomorphism and with a distinctively curvilinear vascular pattern.

ICO-O code 8811/3

Synonym

Myxoid malignant fibrous histiocytoma.

Epidemiology

Myxofibrosarcoma is one of the most common sarcomas in elderly patients with a slight male predominance. Although the overall age range is wide, these neoplasms affect mainly patients in the sixth to eighth decade, whereas they are exceptionally rare under the age of 20 years {1413,1422,2236}.

Sites of involvement

The majority of these tumours arise in the limbs including the limb girdles (lower > upper extremities), whereas they are seen only rarely on the trunk, in the head and neck area, and on the hands and feet {1413,1422,2236}. Origin in the retroperitoneum and in the abdominal cavity is extremely uncommon, and most lesions with myxofibrosarcoma-like features in these locations represent dedifferentiated liposarcomas {67,955,1389}. Notably, about two-thirds of cases develop in dermal/subcutaneous tissues, with the remainder occurring in the underlying fascia and skeletal muscle.

Clinical features

Most patients present with a slowly enlarging and painless mass. Local, often repeated recurrences occur in up to 50 to 60% of cases, unrelated to histological grade. In contrast, metastases and tumour associated mortality are closely related to tumour grade. Whereas none of the low grade neoplasms metastasizes, intermediate and high grade neoplasms may develop metastases in about 20 to 35% of cases. In addition to pulmonary and osseous metastases,

lymph node metastases are seen in a small but significant number of cases {1413,1422,2236}. Importantly, low grade lesions may become higher grade in subsequent recurrences and hence acquire metastatic potential. The overall 5-year survival rate is 60-70%.

Macroscopy

Superficially located neoplasms typically consist of multiple, variably gelatinous or firmer nodules, whereas deep seated neoplasms often form a single mass with an infiltrative margin. In high grade lesions areas of tumour necrosis are often found.



Fig. 2.84 Superficially located, low grade myxofibrosarcoma with multinodular growth pattern and gelatinous, myxoid cut surface.

Histopathology

Myxofibrosarcoma shows a broad spectrum of cellularity, pleomorphism, and proliferative activity; however, all cases share distinct morphological features, particularly multinodular growth with incomplete fibrous septa, and a myxoid stroma composed of hyaluronic acid. The low grade end of the morphological spectrum is characterized by hypocellular neoplasms composed of only few, non-cohesive, plump spindled or stellate tumour cells with ill defined, slightly eosinophilic cytoplasm and atypical, enlarged, hyperchromatic nuclei. Mitotic figures are infrequent in low grade lesions. A characteristic finding is the presence of prominent elongated, curvilinear, thin-walled blood vessels with a perivascular condensation of tumour cells and/or inflammatory cells (mainly

lymphocytes and plasma cells). Frequently, so-called pseudolipoblasts (vacuolated neoplastic fibroblastic cells with cytoplasmic acid mucin) are noted. In contrast, high grade neoplasms are composed in large part of solid sheets and cellular fascicles of spindled and pleomorphic tumour cells with numerous, often atypical mitoses, areas of haemorrhage and necrosis. In many cases bizarre, multinucleated giant cells with abundant eosinophilic cytoplasm (resembling myoid cells) and irregular shaped nuclei are noted. However, high grade lesions also focally show features of a lower grade neoplasm with a promi-

nent myxoid matrix and numerous elongated capillaries. The intermediate grade lesions are more cellular and pleomorphic relative to purely low grade neoplasms, but lack extensive solid areas, pronounced cellular pleomorphism and necrosis. Subcutaneous examples of myxofibrosarcoma commonly have very infiltrative margins, often extending beyond what is detected clinically.

Immunophenotype

Tumour cells stain positively for vimentin, and in a minority of cases some spindled or larger eosinophilic tumour cells express muscle specific actin and/or alpha-smooth muscle actin, suggestive of focal myofibroblastic differentiation; desmin, and so-called histiocytic markers (CD68, Mac 387, FXIIIa) are negative {1413}.

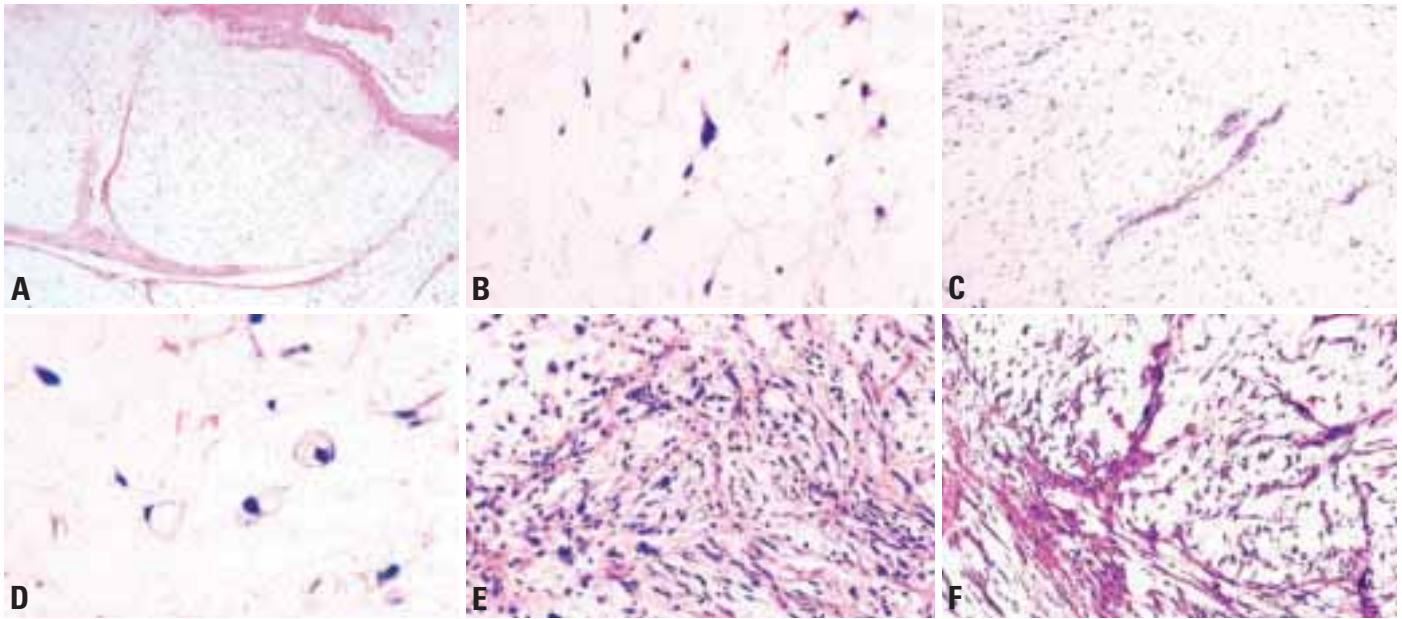


Fig. 2.85 **A** Low grade myxofibrosarcoma showing multinodular growth with a prominent myxoid matrix, **(B)** atypical fibroblastic cells with enlarged and hyperchromatic nuclei on a background of low cellularity, and **(C)** elongated, curvilinear blood vessels as well as pseudolipoblasts **(D)** are frequent findings in low grade myxofibrosarcoma. **E,F** Intermediate grade myxofibrosarcomas retain a myxoid stroma and characteristic vascular pattern, but are more cellular and pleomorphic than low grade lesions.

Ultrastructure

Although fibroblast-like, histiocyte-like, and myofibroblast-like cells, multinucleated giant cells and undifferentiated mesenchymal cells have been described in the past {732,1117,1209}, the majority of cells in myxoid areas show ultrastructural features of a fibroblastic differentiation (fusiform or oval tumour cells with elongated, occasionally clefted nuclei containing a prominent, often dilated rough endoplasmic reticulum) with secretory activity within a myxoid matrix {1413}.

Genetics

Cytogenetic aberrations have been detected in 25 cases diagnosed as myxoid MFH or myxofibrosarcoma {1477}. In general, the karyotypes tend to be highly complex, with extensive intratumoral heterogeneity and chromosome numbers in the triploid or tetraploid range in the majority of cases {1317,1477,1486,1635,1957}. No specific aberration has emerged, but ring chromosomes have been reported in five cases. In one case the ring chromosome was shown to originate from 20q {1402}. Genomic imbalances, as detected by comparative genomic hybridization (CGH), frequently include loss of 6p, and gain of 9q and 12q {1957}.

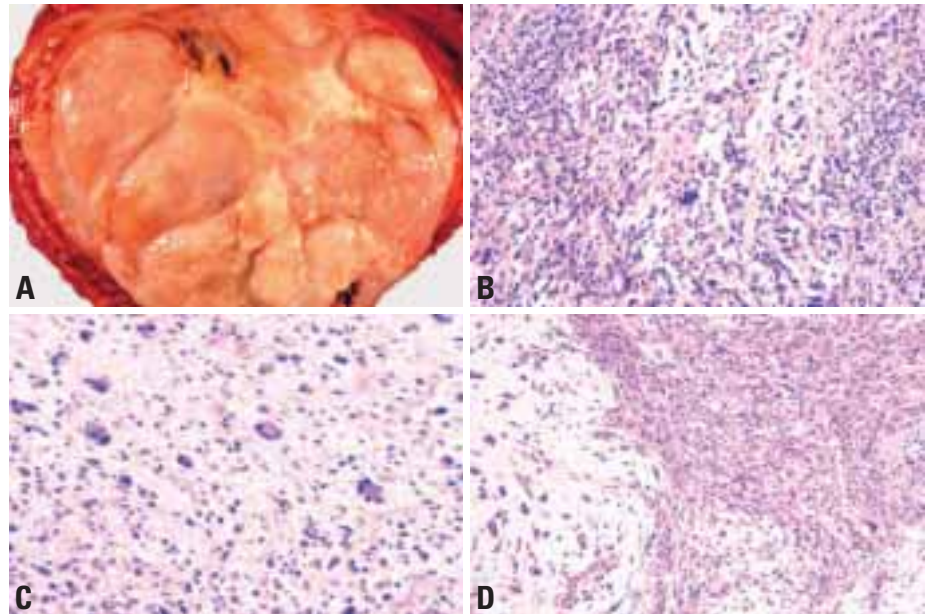


Fig. 2.86 High grade myxofibrosarcoma. **A** Variegated gross appearance with fleshy, gelatinous and yellow-orange areas of necrosis. **B** High grade myxofibrosarcoma with features of a high grade, MFH-like sarcoma and **(C)** frequent multinucleated giant cells with abundant eosinophilic cytoplasm. **D** Focally, areas of lower grade myxofibrosarcoma with a prominent myxoid matrix are usually present in high grade myxofibrosarcoma.

Prognostic factors

Whereas depth of the lesions and grade of malignancy do not influence the high rate of local recurrence, the percentage of metastases and tumour associated mortality are much higher in deep seated and high grade neoplasms {1413,1422, 2236}. A local recurrence

within less than 12 months increases the tumour associated mortality {1413, 1422}. Proliferative activity, the percentage of aneuploid cells, and tumour vascularity are associated with the histological tumour grade, but no clear relation with the clinical outcome has been found {1409,1413}.

Low grade fibromyxoid sarcoma

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Definition

Low grade fibromyxoid sarcoma is a distinctive variant of fibrosarcoma, characterized by an admixture of heavily collagenized and myxoid zones, deceptively bland spindled cells with a whorling growth pattern and arcades of curvilinear blood vessels.

ICD-O code 8811/3

Synonyms

Hyalinizing spindle cell tumour with giant rosettes; fibrosarcoma, fibromyxoid type.

Epidemiology

Low grade fibromyxoid sarcomas are rare sarcomas, with fewer than 150 reported cases {304,507,563,619,621,699,742,813,1053,1074,1217,1268,1417,1552,1939,2077,2150,2296}. It is difficult, however, to estimate the exact incidence of low grade fibromyxoid sarcoma, as many tumours go unrecognized.

Low grade fibromyxoid sarcomas occur equally in men and women and typically affect young adults (median age at presentation 34 years). However, patients of any age may be involved and up to 19% of cases occur in patients younger than 18 years of age {699}.

Sites of involvement

Low grade fibromyxoid sarcomas typically occur in the proximal extremities or trunk, but may occur in unusual locations such as the head or retroperitoneum. The overwhelming majority of cases occur in a subfascial location. They are often large at the time of diagnosis.

Clinical features

Up to 15% of patients report a pre-biopsy duration of over 5 years. Low grade fibromyxoid sarcomas typically present as a painless deep soft tissue mass.

Histopathology

Classical low grade fibromyxoid sarcoma

Low grade fibromyxoid sarcomas show an admixture of heavily collagenized, hypocellular zones and more cellular myxoid nodules. Short fascicular and characteristic whorling growth patterns are seen, with the latter pattern often most apparent at the transition from collagenous to myxoid areas. The vasculature of low grade fibromyxoid sarcomas consists of both arcades of small vessels, and arteriole-sized vessels with perivascular sclerosis. The cells of low grade fibromyxoid sarcomas are very bland, with only scattered hyperchromatic cells. Mitoses are very scarce.

Approximately 10% of cases show areas with increased cellularity and nuclear atypia, similar to that seen in usual-type fibrosarcomas of intermediate grade.

Low grade fibromyxoid sarcoma with giant collagen rosettes

Approximately 40% of otherwise typical low grade fibromyxoid sarcomas show the focal presence of poorly formed collagen rosettes, consisting of a central core of hyalinized collagen surrounded by a cuff of epithelioid fibroblasts. In that subset of low grade fibromyxoid sarcomas where these collagen rosettes are particularly prominent and well formed, the term "hyalinizing spindle cell tumour with giant rosettes" has been applied {1217}. It has been recently shown that the behaviour of low grade fibromyxoid sarcomas with and without giant collagen rosettes are identical {699,2296}.

Immunohistochemistry and ultrastructure

Immunohistochemically, low grade fibromyxoid sarcomas typically express only vimentin, consistent with fibroblastic differentiation. Myofibroblastic differentiation, as reflected by focal smooth muscle actin expression may be seen on occasion. Low grade fibromyxoid sarco-

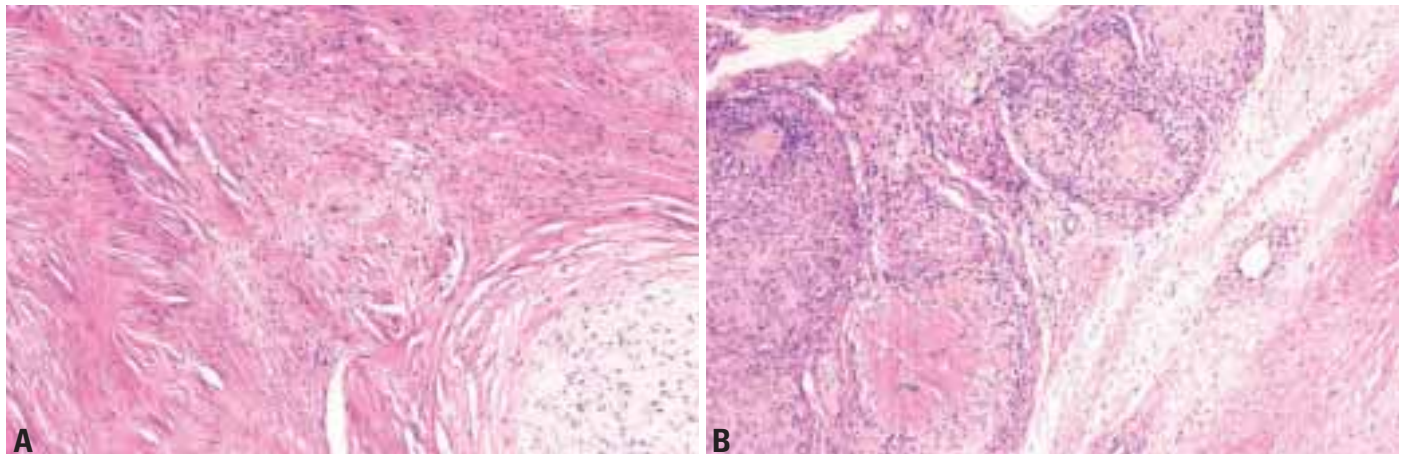


Fig. 2.87 **A** Low grade fibromyxoid sarcoma showing abrupt transition from hyalinized to myxoid nodules. **B** Low grade fibromyxoid sarcoma with numerous giant collagen rosettes (hyalinizing spindle cell tumour with giant rosettes).

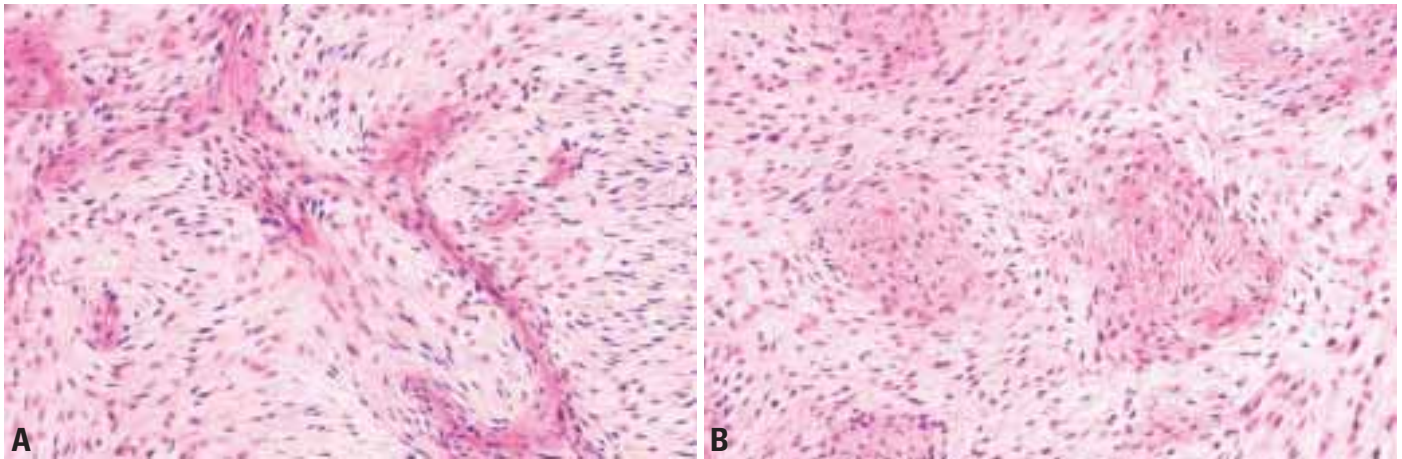


Fig. 2.88 **A** Low grade fibromyxoid sarcoma showing arcades of blood vessels. **B** Low grade fibromyxoid sarcoma with early rosette formation.

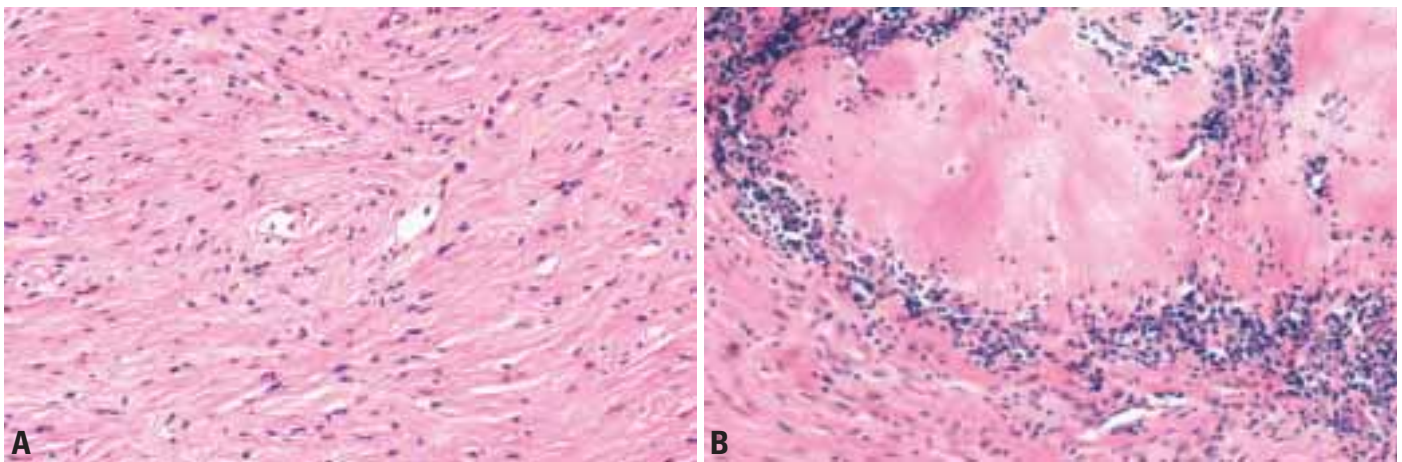


Fig. 2.89 **A** Low grade fibromyxoid sarcoma consisting of very bland spindle cells embedded in a densely collagenous background. **B** In cases with giant cell "rosettes", the tumour cells are arranged in cuffs around nodules of hyaline collagen.

mas almost never express desmin, S100 protein, cytokeratins, epithelial membrane antigen or CD34 [699,813,1552]. Ultrastructural studies have also shown almost exclusively fibroblastic differentiation both in classical low grade fibromyxoid sarcoma and in rosette-containing variants [1565].

Genetics

Excluding cases published as "myxoid malignant fibrous histiocytoma" or "myxofibrosarcoma", only three low grade fibromyxoid sarcomas with chromosome aberrations have been reported [1477]. One had a balanced translocation as the sole aberration [1868]. The two others had supernumerary ring chromosomes, in one case shown by comparative genomic hybridization to consist of chro-

somes 7 and 16 material [1436]. Supernumerary ring chromosomes have been found in many other low grade mesenchymal tumours, including myxofibrosarcoma.

Prognostic factors

There has been a recent evolution in our understanding of the behaviour of low grade fibromyxoid sarcomas. Although the original series of Evans and Goodlad et al suggested that low grade fibromyxoid sarcomas were paradoxically aggressive sarcomas, with a local recurrence rate of 68%, a metastatic rate of 41% and a death rate of 18%, these were retrospective studies [621,813]. Almost all of the approximately 30 patients reported with low grade fibromyxoid sarcoma in these earlier studies were origi-

nally diagnosed with, and treated for a benign lesion. However, a recent large series of prospectively diagnosed low grade fibromyxoid sarcomas showed recurrences, metastases, and death from disease in only 9%, 6% and 2% of patients, respectively [699], although, the median follow-up was only just over 4 years. However, low grade fibromyxoid sarcoma may metastasize many years after initial diagnosis and indefinite clinical follow-up is indicated for patients with this disease. Although the presence of small areas of higher grade fibrosarcoma within otherwise typical low grade fibromyxoid sarcoma has not been shown to be an adverse prognostic factor, the significance of larger high grade areas remains to be determined.

Sclerosing epithelioid fibrosarcoma

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L.G. Kindblom W.M. Molenaar

Definition

Sclerosing epithelioid fibrosarcoma (SEF) is a distinctive variant of fibrosarcoma, composed of epithelioid tumour cells arranged in nests and cords that are embedded within a sclerotic collagenous matrix, thus simulating a poorly differentiated carcinoma or sclerosing lymphoma.

ICD-O code 8810/3

Epidemiology

SEF is a very rare fibrosarcoma variant with a wide age spectrum (median age 45 years) and equal sex distribution {1388}. Approximately 25 additional cases of SEF have been reported {72, 86,347,629,791,1773} since the original series of 25 cases was published {1388}.

Sites of involvement

Most cases are located in the lower extremities and limb girdles, followed by the trunk, upper extremities, and the head and neck area. SEF is invariably deep-seated, frequently impinging upon but rarely invading underlying bone {72, 1388}.

Clinical features

Patients present with a mass of variable duration; in one-third of cases the mass has enlarged noticeably and is painful.

Macroscopy

Size is highly variable, ranging from 2 – 22 cm, with median size of 7-10 cm {72, 1388}. SEF is usually well circumscribed, lobulated or multinodular with a firm, whitish cut surface. Myxoid, cystic, and calcified areas may be seen as well {1388}. Necrosis is uncommon.

Histopathology

Overall, SEF is densely sclerotic, containing nests, strands and acini of small epithelioid cells with scant clear to eosinophilic cytoplasm and uniform oval, round or angulated bland nuclei having little mitotic activity. The abundant collagenous matrix is deeply acidophilic and variably arranged in thick fibrous bands, a delicate lace-like pattern, and fibrous, hyalinized zones reminiscent of a scar or fibroma. Less prominent spindled fascicular areas of conventional low grade fibrosarcoma and hypocellular myxoid zones resembling myxoma or myxofibrosarcoma are also seen, as well as degenerative myxoid cysts and foci of metaplastic bone and calcification. SEF often has a haemangiopericytoma-like vasculature. Despite being well delineated, vascular invasion may be seen along peripheral tumour margins.

Immunophenotype

Vimentin immunostains are consistently positive whereas stains for CD34, leuko-

cyte markers, HMB45, CD68, desmin, GFAP, and TP53 are negative {72,1388}. Focal, weak immunostaining may be seen in a minority of cases with EMA, S100 protein and more rarely for cytokeratins {1388}.

Ultrastructure

The lesional cells display features of fibroblasts {72,1388}, including parallel arrays of rough endoplasmic reticulum filled with granular material and prominent networks of intermediate filaments that may form perinuclear whorls {1388}.

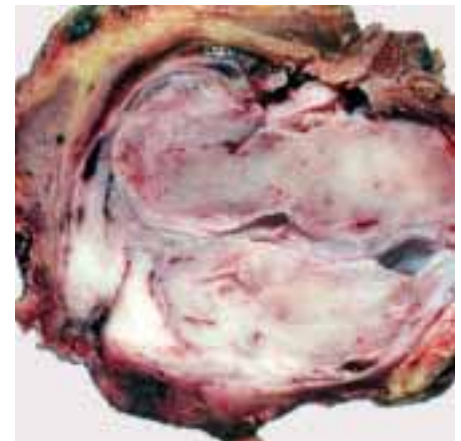


Fig. 2.90 Deep-seated, well circumscribed, extensively fibrous sclerosing epithelioid fibrosarcoma.

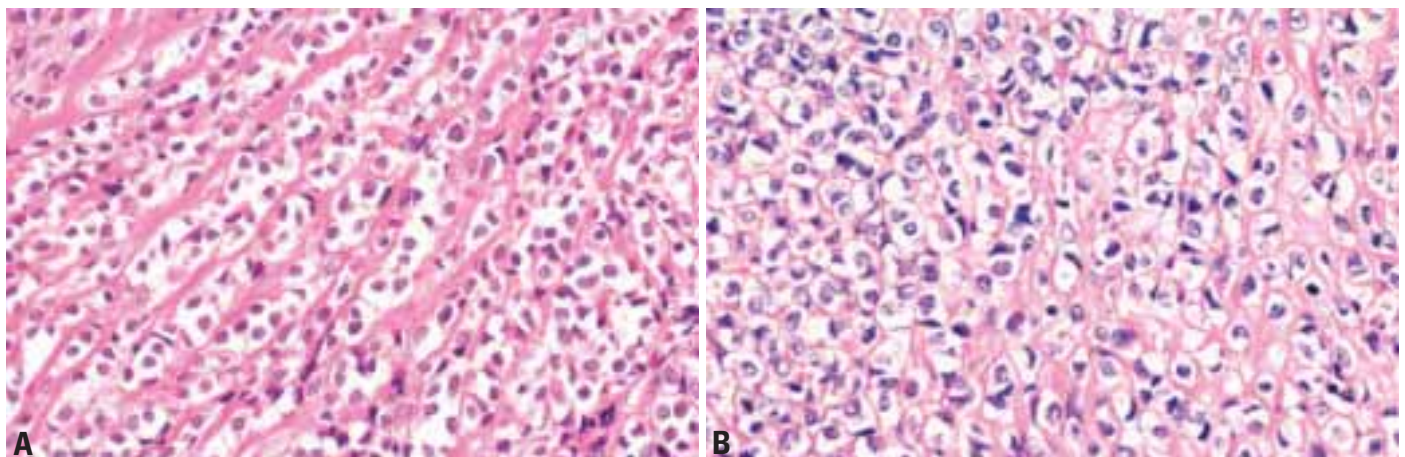


Fig. 2.91 Typical examples of sclerosing epithelioid fibrosarcoma showing cells arranged in (A) cords and in (B) nests.

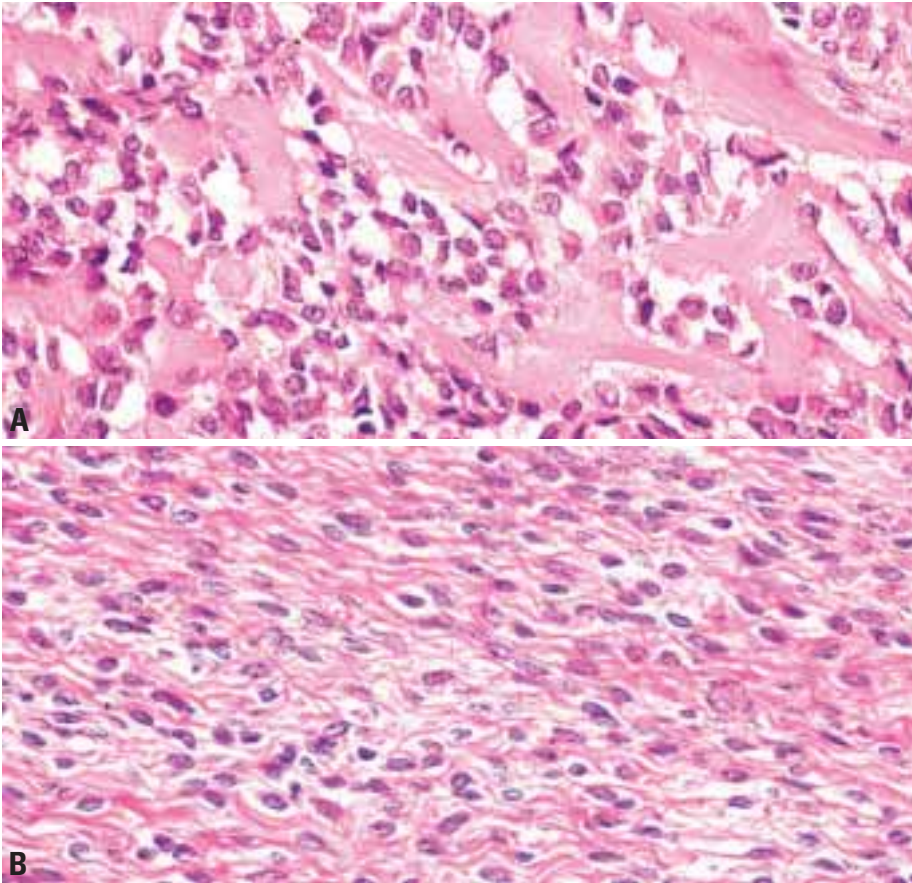


Fig. 2.92 **A** Sclerosing epithelioid fibrosarcoma (SEF) showing cells arranged in alveolae. **B** Area of low grade conventional fibrosarcoma in an SEF.

Genetics

A sclerosing epithelioid fibrosarcoma from a 14-year-old boy showed a complex karyotype with amplification of 12q13 and 12q15, including the *HMGIC* gene, and rearrangement of band 9p13, which has also been reported in a complex karyotype in a case of adult fibrosarcoma {791,1263}. A second case showed a different karyotype with involvement of Xq13, 6q15 and 22q13 {534}.

Prognostic factors

More than 50% of patients develop one or more local recurrences and more than 40% have metastases at median intervals of 5 and 8 years, respectively {1388}. Metastases are usually to lungs, pleura and bone. After 11 years, half of the patients are either dead of disease or have persistent or recurrent tumour {1388}. Somewhat higher rates of metastases and tumour death have recently been reported and may well be due to

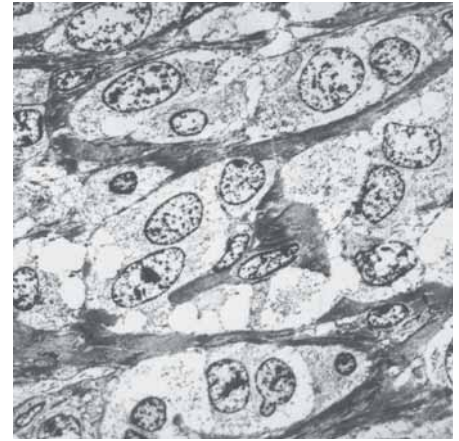


Fig. 2.93 EM features of sclerosing epithelioid fibrosarcoma. Epithelioid fibroblasts are arranged in cords and surrounded by abundant collagen.

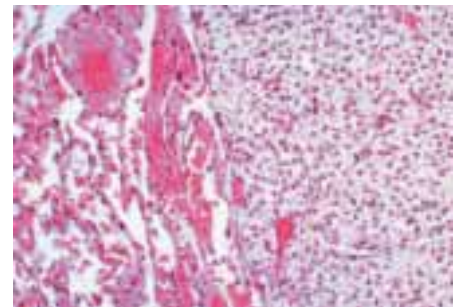


Fig. 2.94 Sclerosing epithelioid fibrosarcoma metastasis to the lung.

larger average tumour size, intracranial location, and potential referral bias {72}. Adverse prognostic factors include proximal tumour site, larger tumour size, male sex, local recurrences, and metastases {1388}.

