



CHAPTER 3

So-called Fibrohistiocytic Tumours

Over the past 10 years, the concept of fibrohistiocytic differentiation has been challenged and is now regarded as a poorly defined morphological descriptor of histiocytic differentiation. Pleomorphic malignant fibrous histiocytoma (MFH) was previously regarded as a distinct tumour type representing the most common adult soft tissue sarcoma. Today, this term is synonymous with undifferentiated pleomorphic sarcoma, which has become a diagnosis of exclusion accounting for less than 5% of adult sarcomas. Similarly, the morphological features formerly regarded as characteristic of the giant cell and inflammatory variants of MFH are shared by a variety of other, specific tumour types. Myxofibrosarcoma (formerly known as myxoid MFH) and so-called angiomatoid MFH remain as distinctive and discrete entities (see Chapters 2 and 9).

Cutaneous fibrous histiocytomas, dermatofibrosarcoma protuberans (best classified as a fibroblastic neoplasm) and atypical fibroxanthoma are described separately in the Skin volume. Since the localized and diffuse forms of giant cell tumour of tendon sheath have more in common with the descriptive category of fibrohistiocytic lesions than with true synovium, they are for now included in this chapter.

Giant cell tumour of tendon sheath

N. de St. Aubain Somerhausen
P. Dal Cin

The term giant cell tumour of tendon sheath encompasses a family of lesions most often arising from the synovium of joints, bursae and tendon sheath {1027}. These tumours are usually divided according to their site (intra- or extra-articular) and growth pattern (localized or diffuse) into several subtypes, which differ in their clinical features and biological behaviour.

Definition

The localized type of giant cell tumour of tendon sheath is a circumscribed proliferation of synovial-like mononuclear cells, accompanied by a variable number of multinucleate osteoclast-like cells, foam cells, siderophages and inflammatory cells, most commonly occurring in the digits.

ICD-O code 9252/0

Synonyms

Tenosynovial giant cell tumour, localized type, nodular tenosynovitis.

Epidemiology

The localized form is frequent and the most common subset of giant cell tumours. Tumours may occur at any age but usually between 30 and 50 years, with a 2:1 female predominance {2163}.

Sites of involvement

Localized giant cell tumours occur predominantly in the hand where they probably represent the most common neoplasm. Approximately 85% of the tumours occur in the fingers, in close proximity to the synovium of the tendon sheath or interphalangeal joint. The lesions may infrequently erode or infiltrate the nearby bone {2160}, or rarely involve the skin.

Other sites include the wrist, ankle / foot, knee, and very rarely the elbow and the hip {1492,2163}.

Clinical features

The most common presenting symptom is that of a painless swelling. The tumours develop gradually over a long period and a preoperative duration of several years is often mentioned. Antecedent trauma is reported in a variable number of cases (from 1 to 50%) {1492,2163}.

Radiological studies usually demonstrate a well circumscribed soft tissue mass, with occasional degenerative changes of the adjacent joint or erosion of the adjacent bone {1046}.

Aetiology

Tenosynovial giant cell tumours initially were regarded as an inflammatory

process based on animal models, the common history of trauma, the predilection for the first three fingers of the right hand {1492} and one X-inactivation study suggesting polyclonality {2295}. However, the finding of aneuploidy in some cases {7}, the demonstration of clonal chromosomal abnormalities {1774}, and the fact that these lesions are capable of autonomous growth strongly support a neoplastic origin.

Macroscopy

Grossly, most localized giant cell tumours are small (between 0.5 and 4 cm), although lesions of greater size may be found in large joints. Tumours are well circumscribed and typically lobulated, white to grey with yellowish and brown areas.

Histopathology

Tumours are lobulated, well circumscribed and at least partially covered by a fibrous capsule. Their microscopic appearance is variable, depending on the proportion of mononuclear cells, multinucleate giant cells, foamy macrophages, siderophages and the amount of stroma. Osteoclast-like cells, which contain a variable number of nuclei (from 3-4 to more than 50), are usually readily apparent but may be

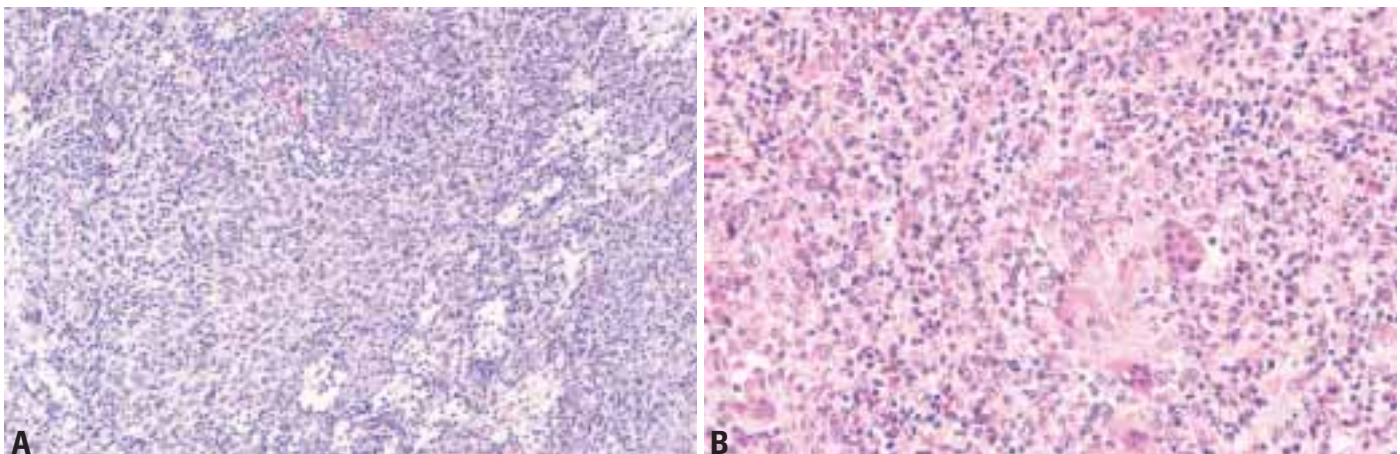


Fig. 3.01 Giant cell tumour of tendon sheath. **A** Typical admixture of histiocytoid cells, foamy cells and lymphocytes. In this case, giant cells are scanty. **B** Typical mononuclear histiocytoid cells with variably prominent eosinophilic cytoplasm and scattered osteoclastic giant cells.

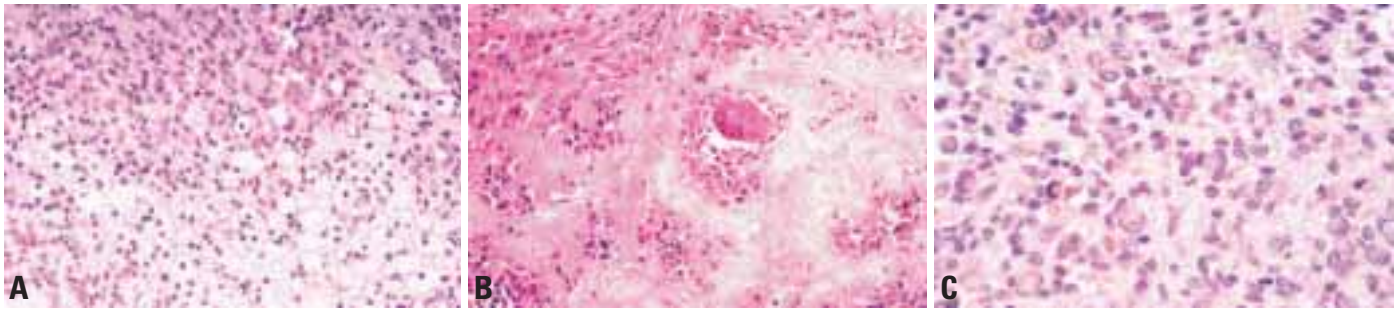


Fig. 3.02 Giant cell tumour of tendon sheath. **A** Most cases show focal collections of xanthoma cells, while others (**B**) show extensive stromal hyalinization. **C** Small, histiocyte-like cells with occasional nuclear grooves and larger cells with vesicular nuclei and abundant eosinophilic cytoplasm, frequently with a rim of haemosiderin.

inconspicuous in highly cellular tumours. Most mononuclear cells are small, round to spindle-shaped. They are characterized by pale cytoplasm and round or reniform, often grooved nuclei. They are accompanied by larger epithelioid cells with glassy cytoplasm and rounded vesicular nuclei. Xanthoma cells are frequent, tend to aggregate locally near the periphery of nodules and may be associated with cholesterol clefts. Haemosiderin deposits are virtually always identified. The stroma shows variable degrees of hyalinization and may occasionally have an osteoid-like appearance. Cleft-like spaces are less frequent than in the diffuse form [2163]. Mitotic activity usually averages 3 to 5 mitoses per 10 HPF but may reach up to 20/10 HPF [2295]. Focal necrosis is rarely seen.

Immunophenotype

Immunohistochemically, mononuclear cells are positive for CD68. Some cells may also express muscle-specific actin

(HHF35). A subset of desmin-positive dendritic cells is reported in up to 50% of cases [705].

Multinucleate giant cells express CD68, CD45 and markers such as tartrate resistant acid phosphatase [449,1590].

Ultrastructure

Ultrastructural studies have revealed an heterogeneous cell population composed of a majority of histiocyte-like cells, accompanied by fibroblast-like cells, intermediate cells, foam cells and multinucleate giant cells [35,2163].

Genetics

Cytogenetic aberrations have been described in 11 giant cell tumours of tendon sheath. A near- or pseudodiploid karyotype was seen in all cases, mostly with simple structural changes [1910]. The short arm of chromosome 1 is frequently involved, with a clustering of breakpoints to the region p11-p13 in 7/11 cases. A recurrent $t(1;2)(p11;q35-36)$ has been identified, but several other

translocation partners have been described, including 3q21, 5q31, and 11q11. In addition, two cases without 1p11-13 rearrangement had translocations involving 16q24, thus possibly representing an alternative primary cytogenetic change. Numerical changes seem to be rare. In particular, it should be noted that gain of chromosomes 5 and 7, which is common in the diffuse type giant cell tumour [1477], has not been described in the localized form [1910].

Prognostic factors

Localized giant cell tumour is a benign lesion with a capacity for local recurrence. Local excision is the treatment of choice. 4 to 30 % of cases recur [1504, 1757,1774] but these recurrence are usually non-destructive and are controlled by surgical reexcision. It has been suggested that recurrences develop most often in highly cellular tumours or lesions with a high mitotic count [1757,2298].

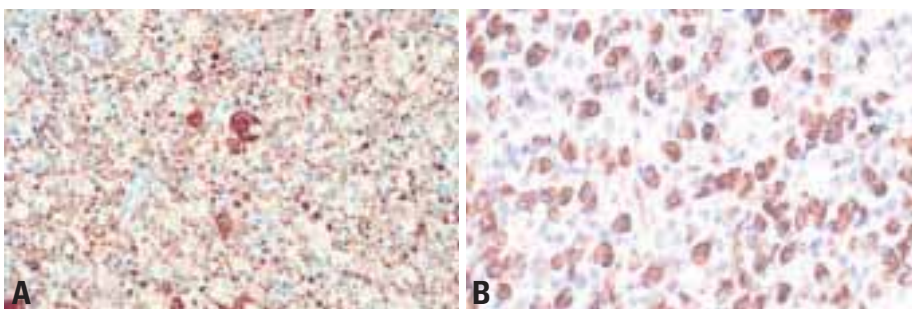


Fig. 3.03 Giant cell tumour of tendon sheath. **A** Localized giant cell tumours of tendons sheath are usually CD 68 positive. **B** Some cases of both localized and diffuse type contain numerous desmin-positive mononuclear cells, sometimes with dendritic cytoplasmic processes.

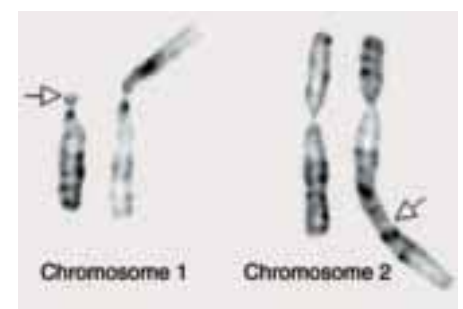


Fig. 3.04 Giant cell tumour of tendon sheath. Partial karyotype showing the characteristic $t(1;2)(p13;q37)$ translocation. Arrows indicate breakpoints.

Diffuse-type giant cell tumour

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Definition

Diffuse-type giant cell tumour is a destructive proliferation of synovial-like mononuclear cells, admixed with multinucleate giant cells, foam cells, siderophages and inflammatory cells. The extraarticular form is defined by the presence of an infiltrative soft tissue mass, with or without involvement of the adjacent joint.

The very uncommon malignant giant cell tumour of tendon sheath is defined by the coexistence of a benign giant cell tumour with overtly malignant areas or by the recurrence of a typical giant cell tumour as a sarcoma.

ICD-O code 9251/0

Synonyms

Pigmented villonodular synovitis, pigmented villonodular tenosynovitis.

Epidemiology

Diffuse-type giant cell tumours tend to affect younger patients than their localized counterpart. The age of patients varies widely but most lesions affect young adults, under the age of 40. There is a slight female predominance {1523, 1984,2164}.

Sites of involvement

Intraarticular lesions affect predominantly the knee (75% of cases), followed by the hip (15%), ankle, elbow and shoulder. Rare cases are reported in the tem-

poromandibular and spinal facet joints {782,1899}. Extraarticular tumours most commonly involve the knee region, thigh and foot. Uncommon locations include the finger, wrist, groin, elbow and toe {87, 1984,2164}.

Most extraarticular tumours are located in periarticular soft tissues but these lesions can be purely intramuscular or predominantly subcutaneous {2164}.

Clinical features

Patients complain of pain, tenderness, swelling or limitation of motion. Haemorrhagic joint effusions are common. The symptoms are usually of relatively long duration (often several years). Radiographically, most tumours present as ill defined peri-articular masses, frequently associated with degenerative joint disease and cystic lesions in the adjacent bone {542}. On magnetic resonance imaging, giant cell tumours show decreased signal intensity in both T1- and T2-weighted images {1036}.

Aetiology

Although these lesions have been regarded as reactive, the presence of clonal abnormalities {1910} and the capacity for autonomous growth are now widely regarded as evidence for a neoplastic origin.

Macroscopy

Diffuse-type giant cell tumours are usually large (often more than 5 cm), firm or

sponge-like. The typical villous pattern of pigmented villonodular synovitis is usually lacking in extraarticular tumours. The latter have a multinodular appearance and a variegated colour, with alternation of white, yellowish and brownish areas.

Histopathology

Most tumours are infiltrative and grow as diffuse, expansile sheets. Their cellularity is variable: compact areas alternate with pale, loose, discohesive zones. Cleft-like spaces are common and appear either as artefactual tears or as synovial-lined spaces. Blood-filled pseudoalveolar spaces are seen in approximately 10% of cases.

In comparison with the localized form, osteoclastic giant cells are less common and may be absent or extremely rare in up to 20% of cases. They are irregularly distributed throughout the lesions and are more easily found around haemorrhagic foci.

The mononuclear component comprises two types of cells: small histiocyte-like cells, which represent the main cellular component, and larger cells. Histiocyte-like cells are ovoid or spindle-shaped, with palely eosinophilic cytoplasm. Their nuclei are small, ovoid or angulated, contain fine chromatin, small nucleoli and frequently display longitudinal grooves. Larger cells are rounded or sometimes show dendritic cytoplasmic processes. Their cytoplasm is abundant, pale to deeply eosinophilic, often contains a

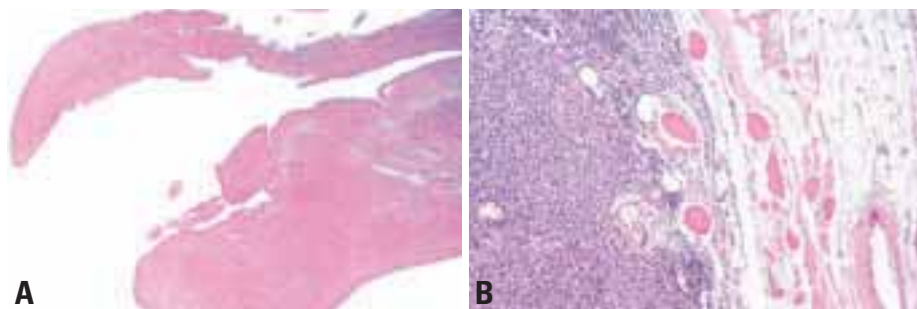


Fig. 3.05 **A** Villous appearance of an intra-articular diffuse-type giant cell tumour. **B** Low magnification of a completely extra-articular tumour showing infiltration of the muscular and adipose tissue.

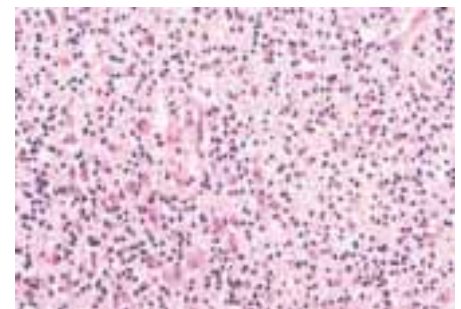


Fig. 3.06 Diffuse-type giant cell tumour with prominent inflammatory component and numerous large dendritic cells with abundant cytoplasm.

peripheral rim of hemosiderin granules and occasionally shows a paranuclear eosinophilic filamentous inclusion. Nuclei are characterized by reniform or lobulated shape, thick nuclear membranes, vesicular chromatin and eosinophilic nuclei. The occasional predominance of these larger cells may obscure the typical features of giant cell tumour and lead to a diagnosis of sarcoma. Sheets of foam cells are frequently observed, usually in the periphery of lesions and variable amounts of haemosiderin are identified in most cases. Giant cell tumours may also contain a significant lymphocytic infiltrate. The stroma shows variable degrees of fibrosis and may appear hyalinized, although this is usually less marked than in the localized form.

Mitoses are usually identifiable and mitotic activity of more than 5 per 10 HPF is not uncommon {1984,2164,2239}.

There have been several reports of typical giant cell tumours recurring as a histologically malignant neoplasms and a few series included primary histologically malignant tumours of the tendon sheath resembling giant cell tumours {187,637,1555,1941,1984}. These neoplasms tended to show significantly increased mitotic rate (more than 20 mitoses / 10 HPF), necrosis, enlarged nuclei with nucleoli, spindling of mononucleated cells, the presence of abundant eosinophilic cytoplasm in histiocyte-like cells, and stromal myxoid change, although none of these features could be used in isolation as a criterion for malignancy {187,637,1984}.

In addition, two cases with banal histology which developed metastatic disease (in the lungs or lymph nodes) have been reported to date {1984,2239}.

Immunophenotype

The immunohistochemical and ultrastructural features of diffuse-type giant cell tumour are similar to those of the localized form. Mononuclear cells are positive for CD68 and other macrophage markers. Desmin stain highlights a population of cells with dendritic features in 35 to 40% of cases; these frequently correspond to the larger eosinophilic cells. Giant cells are positive for CD68 and CD45 {705,1590,1984}.

Genetics

Chromosomal aberrations have been described in 17 cases, all with a near-

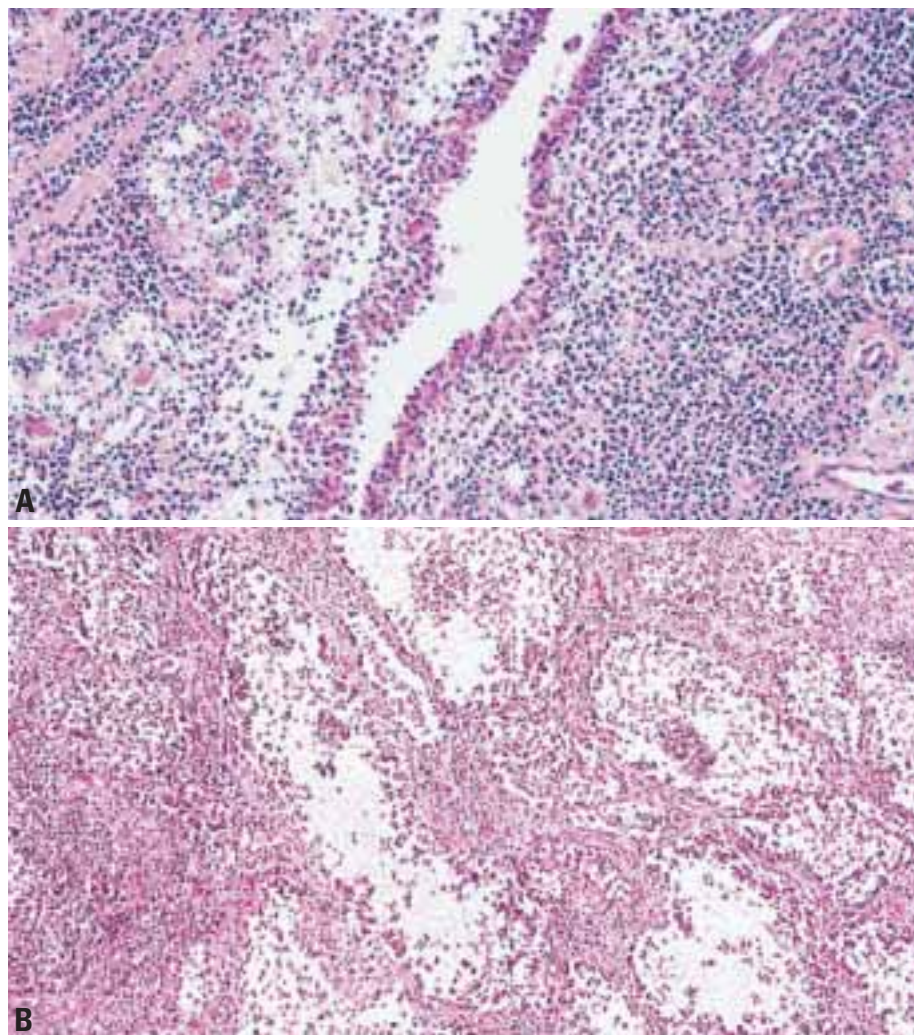


Fig. 3.07 Diffuse-type giant cell tumour. **A** Pseudosynovial or 'pseudoglandular' spaces, surrounded by clusters of xanthoma cells. **B** Pseudoalveolar spaces are commonly seen in diffuse-type giant cell tumours.

pseudodiploid karyotype. Rearrangements of the 1p11-13 region have been detected in eight of them, one had a $t(1;2)(p22;q35-37)$, and one had involvement of band 16q24, suggesting a close cytogenetic relationship with the local-

ized form of giant cell tumour {1910}. One difference, however, between these two entities, is that trisomies for chromosomes 5 and 7, usually as the sole anomalies, have been detected only in diffuse-type giant cell tumours {1477}. The sig-

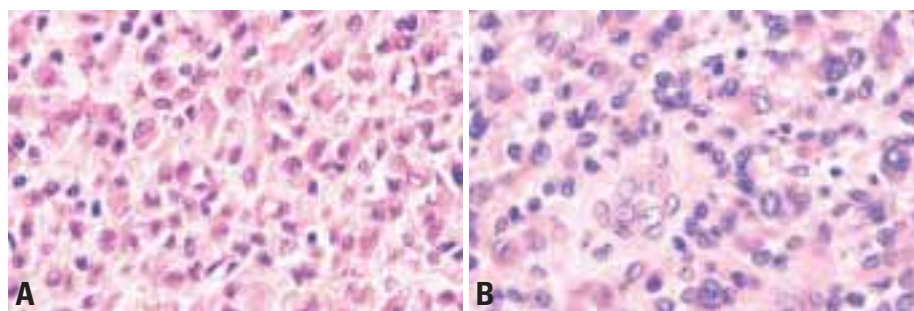


Fig. 3.08 Diffuse-type giant cell tumour. **A** Typical mononuclear histiocyte cells, some of which have prominent eosinophilic cytoplasm. **B** Note frequent nuclear grooves in the histiocyte cells. Some tumour cells have more prominent eosinophilic cytoplasm with haemosiderin granules.

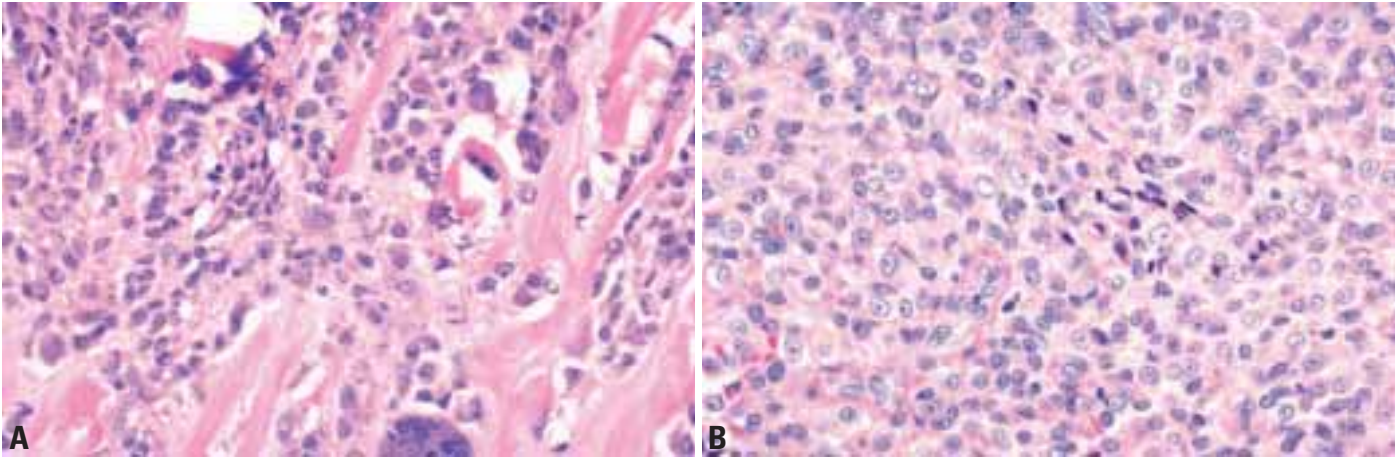


Fig. 3.09 Malignant diffuse-type giant cell tumour. Although there is usually at least focal morphological overlap with usual giant cell tumour (A), closer examination reveals increased cellularity and predominance of atypical large cells with prominent nucleoli (B).

nificance of trisomy 5 and 7 for tumour development in this context is questionable because the same aneuploidies are frequent also in synovial samples from patients with various forms of reactive synovial lesion {1429}.

Prognostic factors

Recurrences are common, often multiple and may severely compromise joint func-

tion. The recurrence rate has been estimated between 18 and 46 % for intra-articular lesions and between 33 and 50% of cases for extraarticular tumours {1899, 1984,2164,2239}. The risk of recurrence does not seem to be correlated with any histological parameter other than positive excision margins. Therefore, diffuse-type giant cell tumours should be regarded as locally aggressive but nonmetasta-

sizing neoplasms and wide excision is the treatment of choice.

Although the number of cases is limited, malignant giant cell tumours of tendon sheath showing obvious sarcomatous areas are potentially aggressive and may give rise to pulmonary metastasis {187, 1555,1941,1984}.

Deep benign fibrous histiocytoma

J.M. Coindre

Definition

A benign fibrous histiocytoma, which develops entirely within subcutaneous tissue, deep soft tissues or in parenchymal organs.

ICD-O code 8830/0

Epidemiology

Deeply located fibrous histiocytomas are rare. Based on the only published series, they represent less than 1% of fibrohistiocytic tumours {673}. Their exact frequency is difficult to determine because

some cases published as deep fibrous histiocytomas may represent solitary fibrous tumours {673,706}. They may develop at any age, but most affect adults over 25 years old, with a predominance in males.

Sites of involvement

The lower limb and the head and neck region are the most common sites. Most cases develop in subcutaneous tissue, but a few cases have been reported in muscle, mesentery, trachea and kidney {673,869,1147,1843}.



Fig. 3.10 Deep benign fibrous histiocytoma tends to be more circumscribed than the cutaneous form and pseudo-encapsulated.

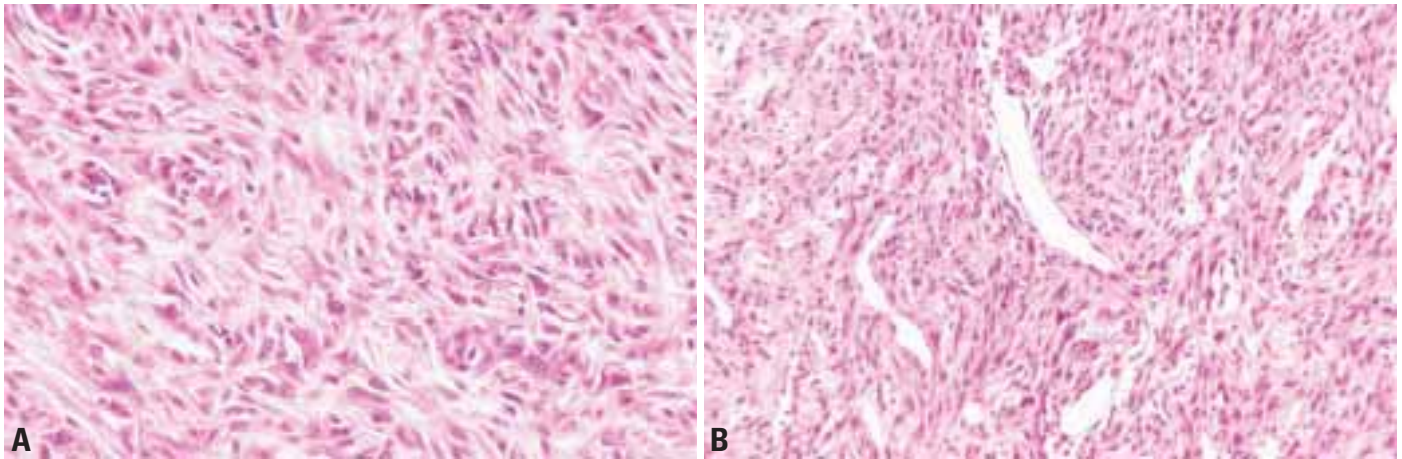


Fig. 3.11 Deep benign fibrous histiocytoma. **A** A monomorphic storiform pattern is usually seen. **B** Branching pericytoma-like vessels are common.

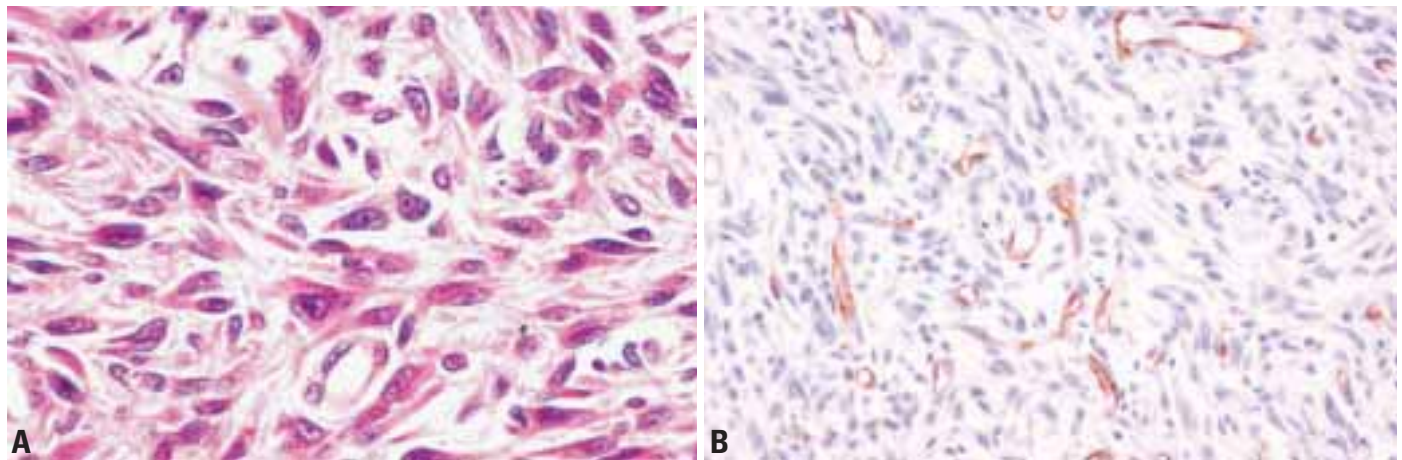


Fig. 3.12 Deep benign fibrous histiocytoma. **A** These lesions show less cytologic polymorphism than their dermal counterparts. **B** Staining for CD34 is most often negative.

Clinical features

Most lesions present as a painless and slowly enlarging mass.

Macroscopy

Contrary to the cutaneous form, deep lesions tend to be well circumscribed and pseudo-encapsulated with occasional areas of haemorrhage. Most lesions are 4 cm or more when resected.

Histopathology

Deep fibrous histiocytomas usually show a prominent storiform pattern, sometimes combined with haemangiopericytoma-like areas.

Contrary to conventional cutaneous lesions, most lesions show monomor-

phism and usually lack secondary elements such as foamy cells and giant cells but usually show scattered lymphocytes. Thus, they more closely resemble the cellular variant of cutaneous fibrous histiocytoma. The tumour cells are cytologically bland and generally spindle-shaped with elongated or plump vesicular nuclei and eosinophilic, ill defined cytoplasm. There is no nuclear pleomorphism or hyperchromasia, and mitoses, although commonly present, are usually less than 5 per 10 high power fields. The stroma may show myxoid change or hyalinization and rarely osteoclast-like giant cells or metaplastic ossification [673,1973]. Small foci of necrosis may be present.

Immunophenotype

Immunohistochemistry shows similar results as in cutaneous lesions with negativity for epithelial markers, desmin and S100 protein. Alpha smooth muscle actin may be positive in some parts of the lesion. CD34 is usually (but not always) negative, but, if positive, solitary fibrous tumour should be considered.

Prognostic factors

Deep fibrous histiocytoma may recur locally [673], particularly if incompletely excised. No metastasis has been reported so far.

Plexiform fibrohistiocytic tumour

A.G. Nascimento
P. Dal Cin

Definition

Plexiform fibrohistiocytic tumour (PFT) is a mesenchymal neoplasm of children, adolescents, and young adults, characterized by fibrohistiocytic cytomorphology, and a multinodular growth pattern. It rarely metastasizes.

ICD-O code 8835/1

Epidemiology

PFT preferentially affects young individuals; mean age at presentation is approximately 14.5 years {603,1782}. The tumour occurs

more often in female than in male patients, with reported female-to-male ratios ranging from 2.5:1 {603} to 6:1 {1782}. PFT has not been reported to occur with greater frequency in any particular race.

Sites of involvement

PFT involves the upper extremities in approximately 65% of cases {603,1782}, with the hands and wrists being affected in about 45% of cases {1782}. The lower extremities are involved in approximately 27% of cases {1782}. PFT rarely occurs in the head and neck region.

Clinical features

PFT usually presents as a small, poorly demarcated, painless dermal or subcutaneous mass that slowly enlarges for months to years {603,1782}. It is clinically characterized by slow growth, frequent local recurrence, and rare regional lymphatic and systemic metastasis {603,1782}.

Macroscopy

PFT is usually a multinodular, firm, poorly circumscribed dermal or subcutaneous mass that rarely exceeds 3 cm.

Histopathology

PFT is composed of small nodules or elongated cellular clusters that are interconnected in a characteristic plexiform arrangement. Three distinct cell types are present in variable amounts: mononuclear histiocyte-like cells, spindle fibroblast-like cells, and multinucleated giant cells. The nodules and clusters are interconnected by spindle cells situated at the periphery of the nodules. Three histologic subtypes are recognized: a fibrohistiocytic subtype composed mainly of nodules of mononuclear histiocyte-like cells and multinucleated giant cells, a fibroblastic subtype composed mainly of elongated clusters and short fascicles of fibroblast-like cells, and a mixed subtype composed of both patterns in equal proportion. Cellular atypia and pleomorphism are minimal, mitotic count frequently is low, and necrosis is absent. Vascular invasion is observed in 10-20% of cases. The nodules and clusters are situated in subcutaneous tissue and deep dermis, but extension into skeletal muscle can occur. In pulmonary metastases, PFT presents as small fibrohistiocytic nodules in subpleural and peribronchiolar locations.

Immunophenotype

PFT displays immunoreactivity for vimentin, CD68 (KP1), and smooth muscle actin {62,783,962,1782,2340}. CD68 immunoreactivity is mainly displayed by multinucleated giant cells and mononu-

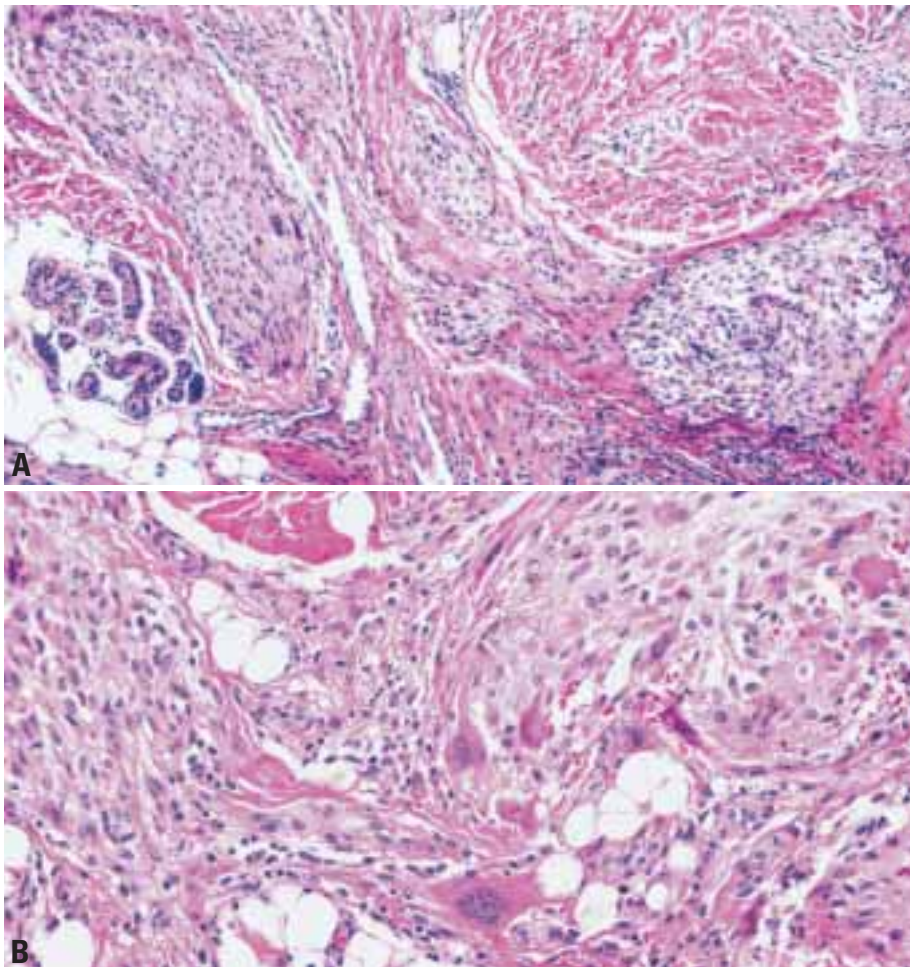


Fig. 3.13 **A** Plexiform fibrohistiocytic tumour is composed of a mixture of small nodules and elongated fascicles that interconnect with each other, forming a characteristic plexiform arrangement. **B** The fibroblastic subtype is composed mainly of elongated clusters and short fascicles of fibroblastlike cells, creating a picture resembling fibromatosis. Scattered multinucleated giant cells are present.

clear histiocyte-like cells {1782,2340}; the fibroblast-like cells stain only rarely with CD68. However, the fibroblast-like cells and occasional histiocyte-like cells stain for smooth muscle actin {62,783,962,2340}.

Ultrastructure

PFT cells have features of myofibroblasts and histiocyte-like cells {62,783,962}, such as abundance of lysosomes, prominent filopodia, and bundles of thin cytofilaments along the cytoplasmic membrane {62}.

Genetics

Only two plexiform fibrohistiocytic tumours with clonal chromosome aberrations have been reported, and no shared chromosome abnormalities were found {1767,1974}.

Prognostic factors

PFT has been associated with a local recurrence rate ranging from 12.5% {1782} to 37.5% {603}, a regional lymph node metastatic rate of 3/61 cases with follow-up {603,1782} and a systemic (lungs only, to date) metastatic rate of 3/61 cases {603}. Such significant metastatic rates likely reflect the bias of consultation practice. No clinicopathologic or genetic factors seem to influence the prognosis of patients with PFT {603,1782}.

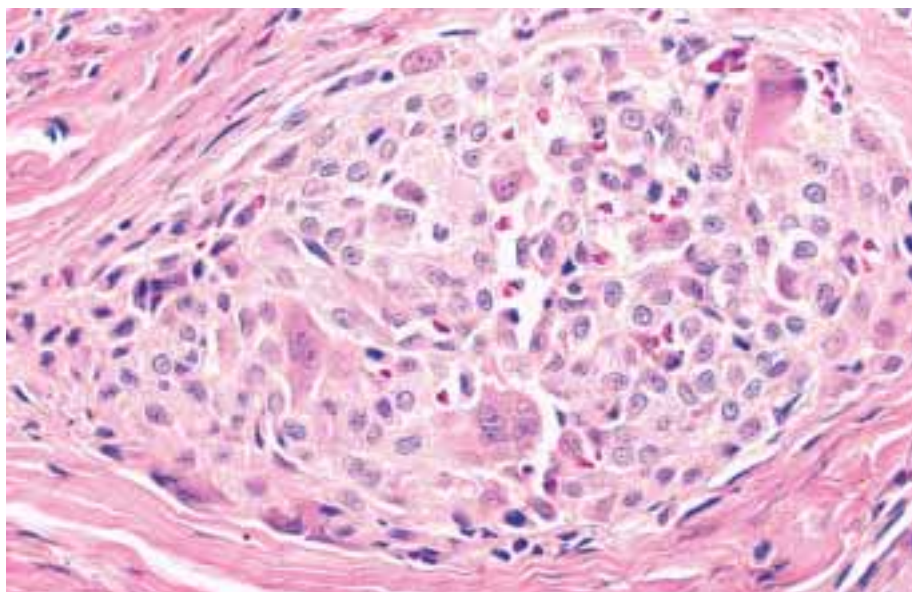


Fig. 3.14 The fibrohistiocytic subtype of plexiform fibrohistiocytic tumour is characterized by nodules of mononuclear histiocyte-like cells and multinucleated giant cells.

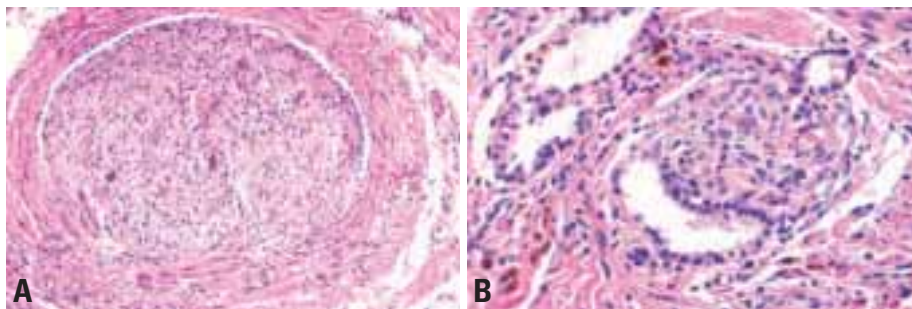


Fig. 3.15 Plexiform fibrohistiocytic tumour. **A** Vascular invasion is occasionally present in 10-20% of cases. **B** Small, peribronchiolar tumoural nodule in pulmonary metastasis of plexiform fibrohistiocytic tumour.

Giant cell tumour of soft tissue

A.G. Nascimento

Definition

Giant cell tumour of soft tissue (GCT-ST) is a primary soft tissue neoplasm that is clinically and histologically similar to giant cell tumour of bone; it very rarely metastasizes.

ICD-O code 9251/1

Synonyms

Osteoclastoma of soft tissue, giant cell tumour of low malignant potential.

Epidemiology

GCT-ST occurs predominantly in the fifth decade of life but can affect patients ranging in age from 5 to 89 years. GCT-ST affects both sexes in equal numbers. GCT-ST does not occur with greater frequency in any particular race {702,1591,1608}.

Sites of involvement

GCT-ST usually occurs in superficial soft tissues of the upper and lower extremities (70% of tumours). Less frequently affected are the trunk (20%) and head and neck region (7%) {702,1591,1608}.

Clinical features

The tumours present as painless growing masses {1591,1608}, with an average duration of symptoms of 6 months {1608}. As in giant cell tumour of bone with soft tissue implants {397}, peripheral mineralization is exceedingly frequent

in GCT-ST, yielding a characteristic radiographic appearance.

Aetiology

No aetiological factors have been identified, but GCT-ST has occurred rarely in patients with Paget disease of bone {758} or after trauma {1608}.

Macroscopy

In the 3 major series of patients with GCT-ST reported to date {702,1591,1608}, tumours ranged in size from 0.7 to 10 cm (mean, 3 cm). Seventy percent of the tumours involved subcutaneous adipose tissue or dermis; only 30% were situated below the superficial fascia. GCT-ST presents as a well circumscribed, mostly solid, nodular mass with a fleshy, red-brown or gray cut surface. Gritty regions of mineralized bone frequently are present at the periphery of the tumours {1591}.

Histopathology

At low magnification, approximately 85% of GCT-STs display a multinodular architecture, with the nodules ranging in size from microscopic dimensions to 15 mm {1608}. The cellular nodules are separated by fibroconnective tissue septa of varying thickness and containing haemosiderin-laden macrophages {1591}. The nodules are composed of a mixture of round to oval cells that are mononuclear and osteoclastlike giant cells that are multinucleated, with both cell types immersed in a richly vascularised stroma. The nuclei in the multinucleate cells are similar to the nuclei in the mononuclear cells.

Mitotic activity generally is present in every GCT-ST; typical mitoses range from 1 to 30 figures per 10 high-power fields {702,1591,1608}. Atypia, pleomorphism, and tumoural giant cells are absent, and necrosis is found rarely {702,1591,1608}. Metaplastic bone formation is present in approximately 50% of the tumours; frequently it is in the form of a peripheral shell of woven bone.

Secondary cystic changes and the formation of blood-filled lakes, changes that are similar to aneurysmal bone cystic changes, are present in approximately 30% of tumours. Unquestionable foci of vascular invasion are part of the histological picture in about 30% of tumours {702,1608}. Additional histological features include stromal haemorrhage (50%) and regressive changes in the form of marked stromal fibrosis and clusters of foamy macrophages (70%).

Immunophenotype

GCT-STs display immunoreactivity for vimentin, CD68, and smooth muscle actin {702,1591,1608}. CD68 strongly marks the multinucleated giant cells; the mononuclear cells show focal staining only. Smooth muscle actin stains a few mononuclear cells and does not mark the multinucleated giant cells. Rarely, tumours react focally with antibodies against keratin and S100 protein {1608}.

Prognostic factors

In patients with clinical follow-up ranging from 34 to 45 months, GCT-ST was associated with a local recurrence rate of 12% and very rare metastasis and death {702,1591,1608}. Incomplete surgical excision is apparently followed by local recurrence {702}. No clinicopathologic factors are currently predictive of metastatic behaviour associated with GCT-ST {702,1591,1608}.

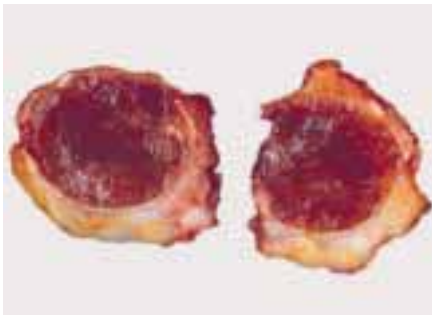


Fig. 3.16 Giant cell tumour of soft tissue, presenting as well circumscribed, mostly solid nodule with a fleshy, red-brown or grey cut surface.

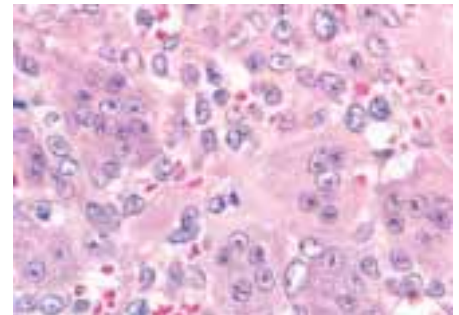


Fig. 3.17 Cellular nodules in giant cell tumour of soft tissue contain a mixture of round / oval mononuclear and multinucleate osteoclast-like giant cells.

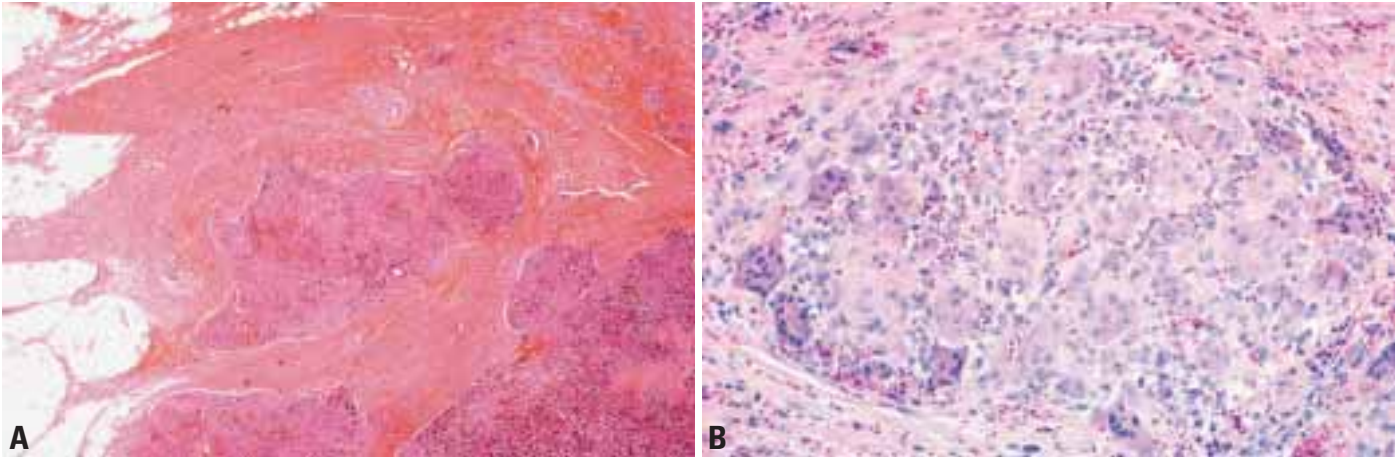


Fig. 3.18 **A** A multinodular growth pattern is present in approximately 85% of giant cell tumours of soft tissues. **B** Typical nodule with peripheral accumulation of osteoclast-like giant cells.

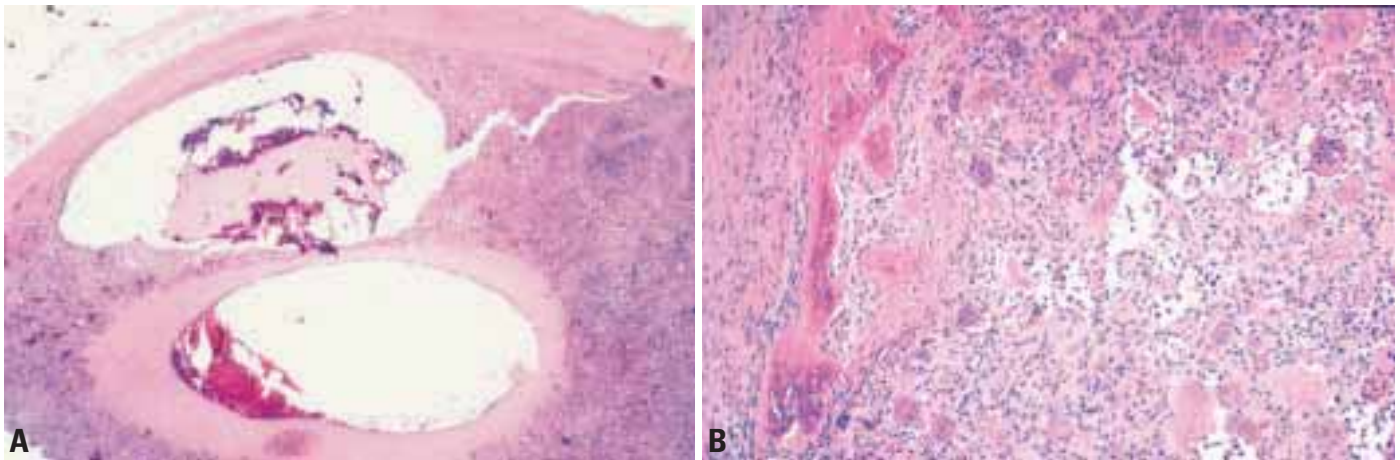


Fig. 3.19 **A** Secondary cystic changes, similar to aneurysmal bone cystic changes, occur in approximately 30% of giant cell tumours of soft tissue. **B** Metaplastic bone, frequently in the form of a peripheral shell of woven bone, is present in approximately 50% of giant cell tumours of soft tissue.

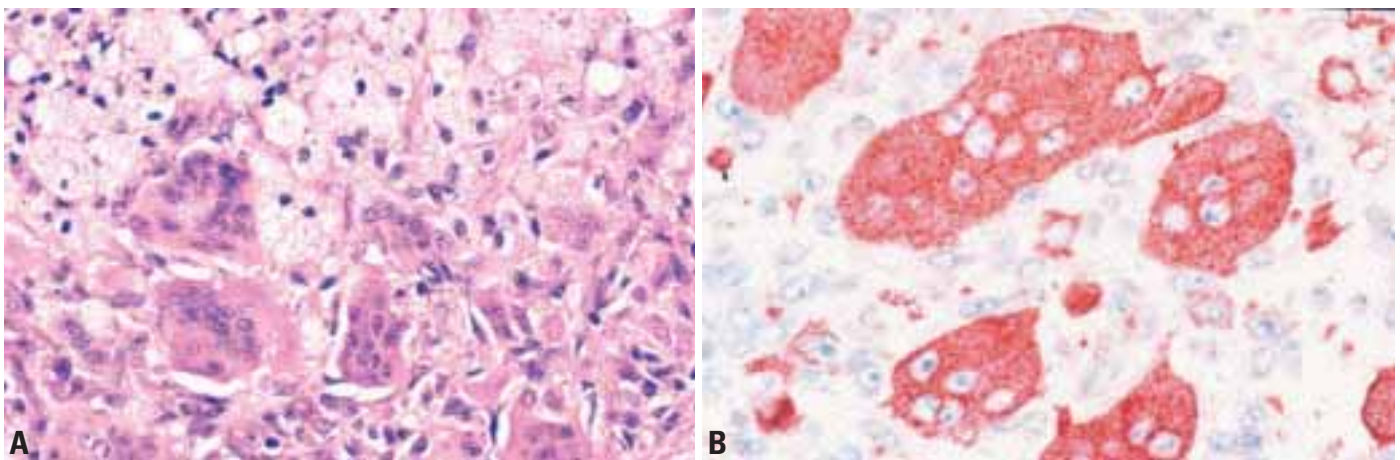


Fig. 3.20 **A** Clusters of foam macrophages reflecting regressive change in a giant cell tumour of soft tissue. **B** CD68 marks the multinucleate, osteoclastlike giant cells and a few of the mononuclear cells in giant cell tumours of soft tissue.

Pleomorphic malignant fibrous histiocytoma / Undifferentiated high grade pleomorphic sarcoma

C.D.M. Fletcher
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W.M. Molenaar

Definition

The term pleomorphic malignant fibrous histiocytoma is now reserved for a small group of undifferentiated pleomorphic sarcomas. Both terms may be used synonymously. Current technology does not show a definable line of differentiation.

ICD-O code 8830/3

Synonyms

Fibroxanthosarcoma {1088}; malignant fibrous histiocytoma, storiform or fibroblastic type; malignant fibrous xanthoma.

Historical annotation

For many years, pleomorphic malignant fibrous histiocytoma (MFH) has been regarded as the prototypical form of MFH and the most common soft tissue sarcoma in adults {599,2233,2237}. Originally defined, based on morphology and tissue culture analysis, as a pleomorphic spindle cell malignant neoplasm showing fibroblastic and facultative histiocytic differentiation, it is now widely accepted that the morphologic pattern known as so-called pleomorphic MFH may be shared by a wide variety of poorly differentiated malignant neoplasms {675}. It is also now agreed that these tumours show no evidence of true histiocytic differentiation. This diagnostic term is now reserved (by those who still use it) for the much smaller group of pleomorphic sarcomas which, by current technology, show no definable line of differentiation {2243}. As a consequence, the apparent incidence of pleomorphic MFH has fallen sharply over the past 10 years and it is possible that this term may disappear altogether at such time as criteria for the diagnosis of pleomorphic sarcomas showing fibroblastic or myofibroblastic differentiation can be reproducibly defined.

Epidemiology

The group of pleomorphic (MFH-like) sarcomas collectively represent the most common types of sarcoma in patients over age 40. The overall incidence

among adults approximates to 1-2 cases per 100,000 patients annually and the incidence increases with age {861}.

Most undifferentiated high grade sarcomas occur in patients over age 40 with peak incidence in the 6th and 7th decades. Rare examples may be encountered in adolescents and young adults. There is a male predominance of approximately 1.2:1.

Sites of involvement

Most undifferentiated high grade pleomorphic sarcomas occur in the extremities (especially the lower limb) and less often the trunk. The majority of cases arise in deep (subfascial) soft tissue, while less than 10% are primarily subcutaneous. A notable exception among pleomorphic sarcomas is dedifferentiated liposarcoma (see p. 38) which is most common in the retroperitoneum.

Clinical features

Undifferentiated high grade pleomorphic sarcomas are typically large deep-seated tumours which show progressive, often rapid enlargement. Only those which grow very rapidly tend to be painful. Around 5% of patients have metastases at presentation, most often to lung. Although little is known about aetiology of these lesions, a subset of pleomorphic sarcomas (<2-3%) arise at the site of prior radiation therapy {1224} and very rare cases arise at the site of chronic ulceration or scarring.

Macroscopy

Most undifferentiated high grade pleomorphic sarcomas are well circumscribed, expansile masses which may appear pseudoencapsulated. Tumour size varies and, to some extent, depends on location with subcutaneous lesions often measuring <5 cm, while retroperitoneal tumours often exceed 20 cm. Most tumours measure between 5 and 15 cm in maximum diameter. Cut surface is variable and may include pale fibrous or fleshy areas, admixed with zones of necrosis, haemorrhage or myxoid

change. Aside from an adjacent well-differentiated component in dedifferentiated liposarcoma, there are no distinctive macroscopic features which correlate reliably with line of differentiation.

Histopathology

Undifferentiated high grade sarcoma is a diagnosis of exclusion following thorough sampling and judicious use of ancillary diagnostic techniques. Tumours in the general category of high grade pleomorphic (MFH-like) sarcomas are very heterogeneous in appearance and also in cellularity, since some cases have an extensive fibrous stroma. These tumours have in common marked cytological and nuclear pleomorphism, often with bizarre tumour giant cells, admixed with spindle cells and often rounded histiocyte-like cells (which may have foamy cytoplasm) in varying proportion {675}. A storiform growth pattern and stromal chronic inflammatory cells are common. The spindle cell component most often appears fibroblastic, myofibroblastic or smooth muscle-like. Tumours showing myogenic differentiation (pleomorphic leiomyosarcoma or rhabdomyosarcoma), as well as carcinoma and melanoma with MFH-like morphology, often have more copious eosinophilic cytoplasm and prominent large polygonal cells. The presence of fascicular spindle cell areas may suggest smooth muscle or nerve sheath differentiation (which needs to be proved immunohistochemically or ultrastructurally). Thorough



Fig. 3.21 Undifferentiated high grade pleomorphic sarcomas are typically deep-seated and large, with a variable cut surface; this case shows fleshy solid areas, necrosis and cystic change.

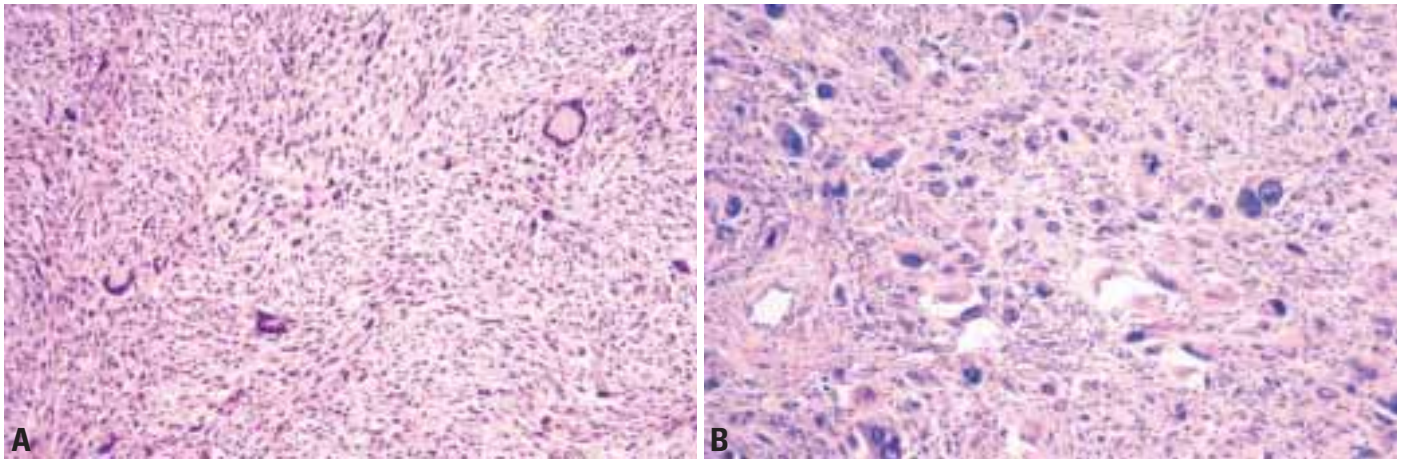


Fig. 3.22 Undifferentiated high grade pleomorphic sarcoma. **A** Note the variable cellularity and striking cytological pleomorphism. This tumour proved to be a malignant peripheral nerve sheath tumour. **B** In other areas this lesion turned out to be pleomorphic liposarcoma with prominent lipoblasts.

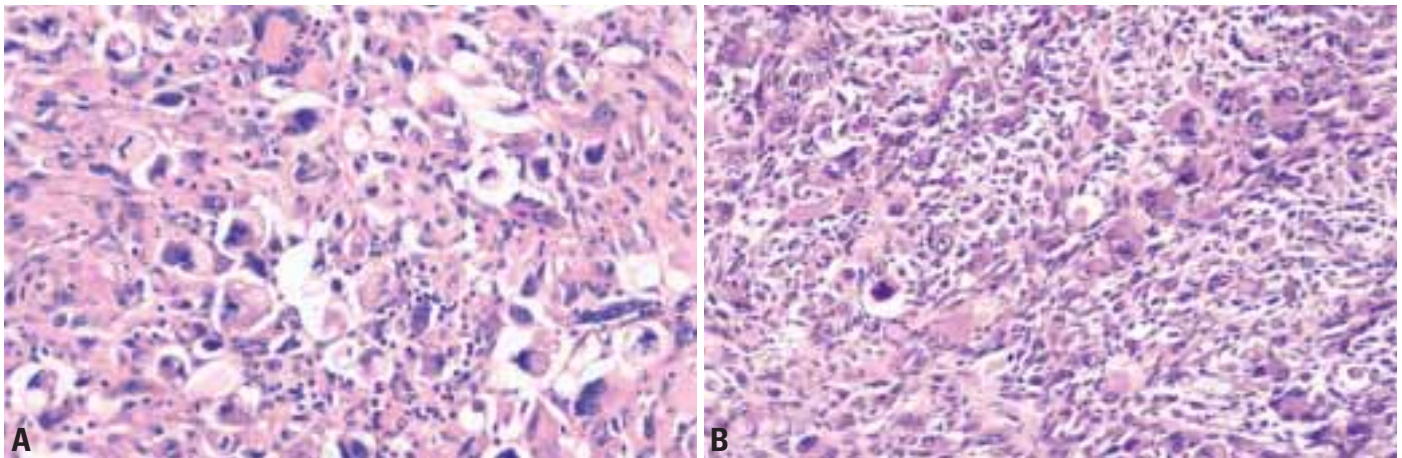


Fig. 3.23 Undifferentiated high grade pleomorphic sarcoma. **A** Note the anaplastic cytology in this unclassified sarcoma. **B** Many tumour cells show a prominent eosinophilic cytoplasm and this case proved to be pleomorphic leiomyosarcoma.

sampling is critical in all cases to check for the presence of lipoblasts or 'malignant' osteoid.

Immunohistochemistry

The widespread introduction of immunohistochemistry has been one of the major factors in demolition of the MFH concept. Most high grade pleomorphic sarcomas show a definable line of differentiation, foremost among which are the pleomorphic variants of leiomyosarcoma, liposarcoma, rhabdomyosarcoma and myxofibrosarcoma, after carcinomas, melanomas and lymphomas have been excluded {675}. Immunohistochemistry was critical in helping to separate the latter non-mesenchymal malignancies. Controversy exists as to the extent of immunopositivity required for a given antigen to define a specific line of differentiation but diagnostic criteria have

been proposed for the different pleomorphic sarcomas and these appear to be reproducible {683,1425}. The presence of just rare cells showing positivity for epithelial or myogenic antigens most often has little significance and does not, of itself, exclude this diagnosis. It is now accepted that histiocytic antigens (such as alpha-1-antitrypsin, alpha-1-antichymotrypsin, lysozyme and CD68) play no useful role in the diagnosis of pleomorphic sarcomas.

Ultrastructure

Electron microscopic findings depend upon the specific type of tumour giving rise to the pleomorphic MFH pattern. Inevitably almost all tumours in this category are poorly differentiated so only a minority of tumour cells may show ultrastructural features of a specific lineage. Many tumour cells show relatively undif-

ferentiated, non-specific fibroblast-like or histiocyte-like features.

Genetics

The genetic aspects of malignant fibrous histiocytomas (MFH) are difficult to evaluate because of the shifting diagnostic criteria used throughout the years. Bearing these shortcomings in mind, cytogenetic aberrations have been detected in more than 50 cases published as storiform or pleomorphic MFH or MFH NOS {1477}. Only a few cases of giant cell or inflammatory MFH have been investigated. 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}. Also near-haploid karyotypes have been reported in a few cases {92}. No specific structur-

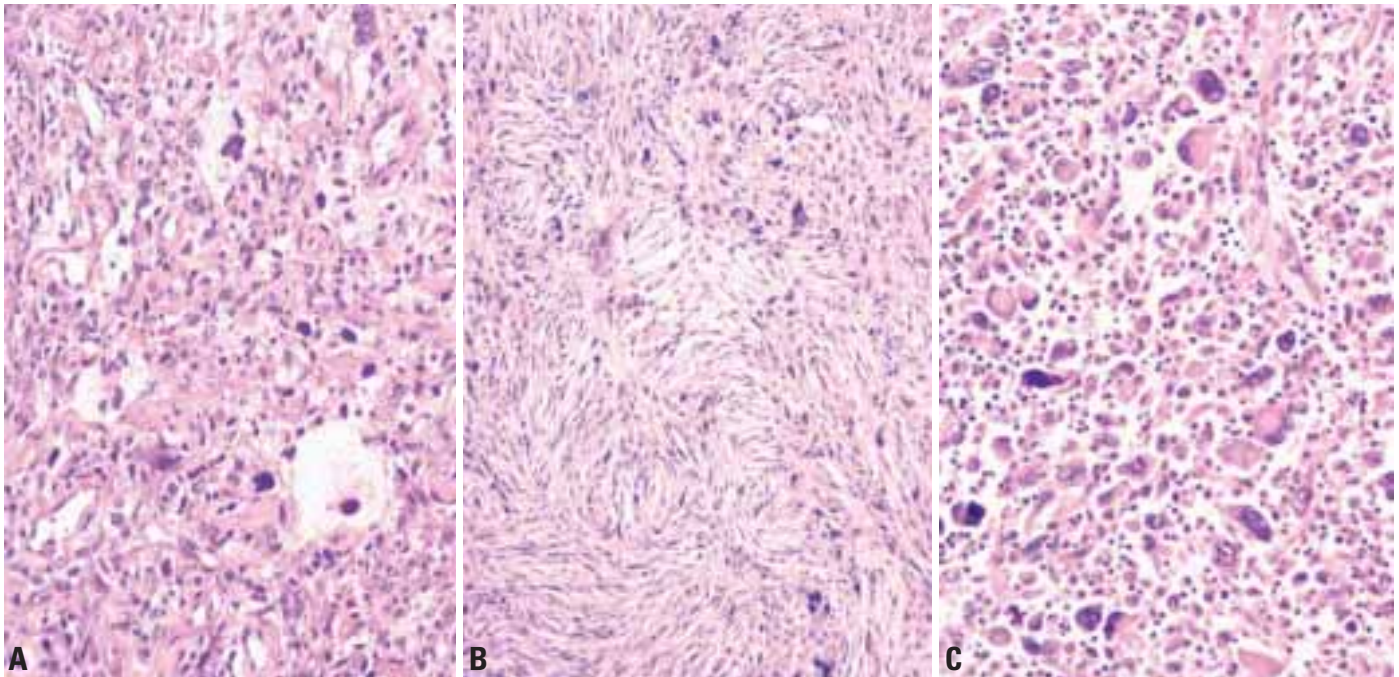


Fig. 3.24 **A** Many pleomorphic sarcomas contain large bizarre cells with foamy cytoplasm, which in the past were mistakenly regarded as histiocytic in nature. **B** A storiform growth pattern is a common feature shared by many of these undifferentiated high grade pleomorphic sarcomas, irrespective of lineage. **C** The presence of polygonal cells with prominent eosinophilic cytoplasm usually suggests myogenic, epithelial or less often melanocytic differentiation. This case proved to be a pleomorphic rhabdomyosarcoma.

al or numerical aberrations have emerged, but telomeric associations, ring chromosomes, and/or dicentric chromosomes are frequent. Such chromosomal abnormalities are, however, common also in other fibrohistiocytic lesions {1854}. Due to the presence of numerous marker chromosomes in most cases, the distribution of genomic imbalances is impossible to assess reliably from cytogenetic data.

Genomic imbalances, as detected by comparative genomic hybridization (CGH), frequently include loss of 2p24-pter and 2q32-qter, and chromosomes 11, 13 and 16 {1219,1311,1651,1957,2094}, as well as gain of 7p15-pter, 7q32, and 1p31.

Several proto-oncogenes mapping to chromosome region 12q13-15 appear to participate in the development of MFH-like pleomorphic sarcomas: *SAS*, *MDM2*,

CDK4, *DDIT3* (a.k.a. *CHOP*), and *HMGIC* (a.k.a. *HMGA2*) have all been reported to be amplified in MFH {172,1772,1842}. In an amplicon at 8p23.1 a candidate gene designated *MASL1* has been found {1842}.

Alterations (mutations and/or deletions) of *TP53*, *RB1* and *CDKN2A* have been suggested to play a critical role in pleomorphic sarcoma development {341,1772,1957,2097,2326}, but no clear relationship with clinical outcome has yet been found. The significance of *HRAS* mutations and their relationship with other genetic changes, such as *TP53* and *MDM2* gene status, remain to be clarified {221,1790,2269}.

Prognostic factors

High grade pleomorphic sarcomas are aggressive with an overall 5-year survival probability of only 50-60% {861,2233}.

However, it has become clear that there are prognostic subgroups among the lesions formerly categorised as pleomorphic MFH {683}. For example, dedifferentiated liposarcoma has a metastatic rate of only 15-20%, high grade myxofibrosarcoma has a metastatic rate of around 30-35%, while pleomorphic myogenic sarcomas (leiomyosarcoma or rhabdomyosarcoma) are especially aggressive with much more frequent metastasis and shorter relapse-free survival {1679}. The clinical and therapeutic benefits of subclassifying pleomorphic sarcomas are only just beginning to be appreciated, hence the approach to subclassification and grading of pleomorphic sarcomas is likely to evolve.

Giant cell malignant fibrous histiocytoma / Undifferentiated pleomorphic sarcoma with giant cells

C.D.M. Fletcher

Definition

Formerly defined as a variant of malignant fibrous histiocytoma (MFH) with prominent osteoclastic giant cells, it is now appreciated that this morphologic pattern may be shared by a variety of tumour types. The term giant cell MFH is currently reserved for undifferentiated pleomorphic sarcomas with prominent osteoclastic giant cells.

ICD-O code 8830/3

Synonyms

Malignant giant cell tumour of soft parts, malignant osteoclastoma, giant cell sarcoma.

Historical annotation

Although formerly defined as a variant of malignant fibrous histiocytoma (MFH) with prominent osteoclastic giant cells {599} (and frequently known as malignant giant cell tumour of soft parts/tissues {61,848}) it is now appreciated that this morphologic pattern may be shared by a variety of tumour types (most notably giant cell tumour of soft tissues, extraskeletal osteosarcoma, leiomyosarcoma and osteoclast-rich carcinoma) {961}. It is difficult to define giant cell MFH as a discrete entity and this diagnosis is gradually disappearing from common usage in soft tissue pathology.

Epidemiology

All of the lesions previously subsumed under this heading are very uncommon. Arguably giant cell tumour of soft tissues (see page 118) is the most frequent. Almost all of the tumours which adopt the pattern known as so-called giant cell MFH occur in older adults with no sex predilection. Rare examples of giant cell tumour of soft tissue occur in children and adolescents.

Sites of involvement

With the exception of giant cell tumour of soft tissues (which shows a predilection for subcutaneous tissue) {702,1591,

1608}, most tumours in this general category occur in deep soft tissue of the limbs or trunk. Organs in which giant cell-rich or osteoclastoma-like carcinomas are most common include pancreas, thyroid, breast and kidney.

Clinical features

Most tumours in this general category present as an enlarging, painless, deep-seated mass without distinctive features.

Macroscopy

With the exception of giant cell tumour of soft tissues, most tumours in this general category are high grade and thus tend to be large tumours with haemorrhage and necrosis. Tumour size is variable but superficially located examples are smaller than those in deep soft tissue.

Histopathology

The features shared by tumours previ-

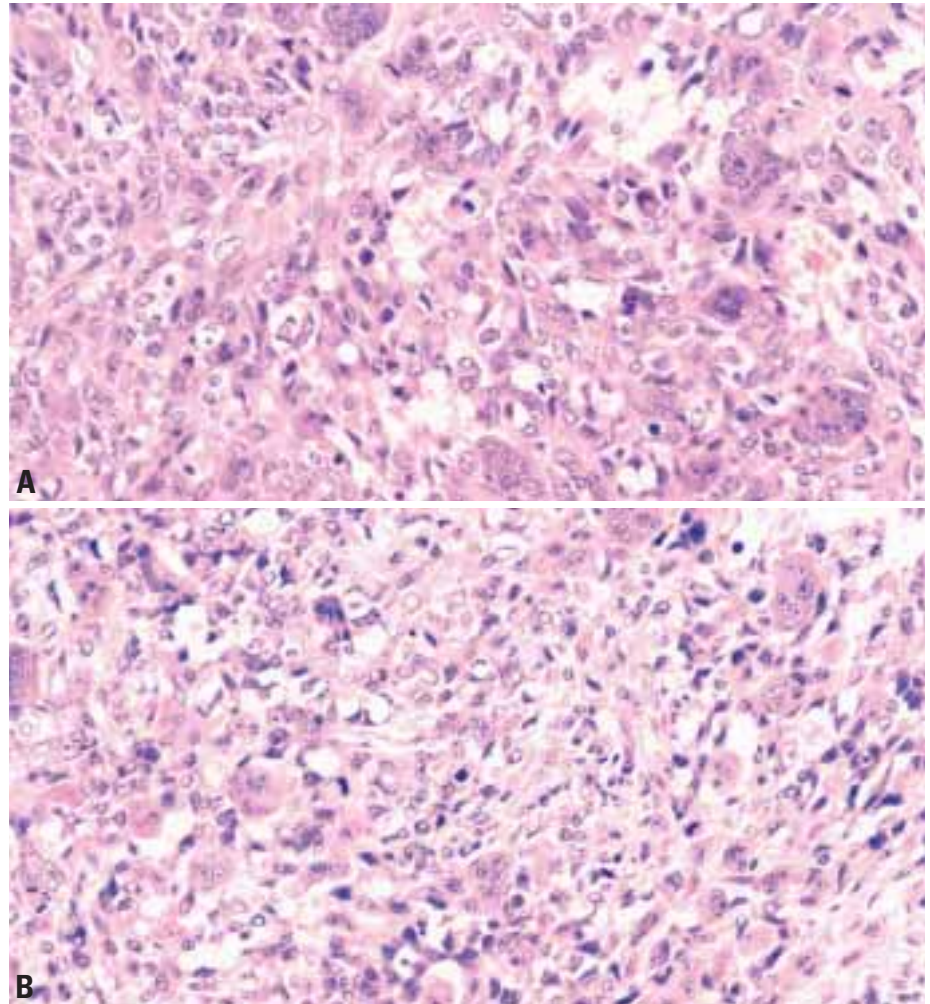


Fig. 3.25 Giant cell MFH. Two tumours showing the pattern often labelled as giant cell MFH, being characterized by atypical spindle-shaped and more epithelioid cells admixed with prominent osteoclastic giant cells. The example on top (A) proved to be anaplastic carcinoma of thyroid, while the lower one (B) was a soft tissue osteosarcoma.

ously labelled as giant cell MFH include variably pleomorphic ovoid-to-spindle-shaped cells and a prominent stromal osteoclastic giant cell reaction. In most (but not all) lesions the giant cell component lacks cytological features of malignancy, but some tumours diagnosed as giant cell MFH were notable for the presence of numerous bizarre multinucleate tumour giant cells.

Aside from these similar (shared) features, morphology is largely determined by the specific tumour type. Giant cell-rich soft tissue osteosarcoma (see page 182) definitionally shows variably prominent 'malignant' osteoid being laid down by cytologically atypical cells {355}. Giant cell tumour of soft tissues (see page 118) usually has a multinodular growth pattern and cytologically resembles giant cell tumour of bone {702, 1591, 1608}. Leiomyosarcoma with prominent osteoclastic giant cells has at least small areas with conventional smooth muscle cytomorphology and a fascicular growth pattern {1411}. Other sarcoma types may occasionally show prominent osteoclastic giant cells {1415}.

Immunohistochemistry

Leiomyosarcoma with prominent osteoclastic giant cells usually shows positivity for smooth muscle actin and desmin in the fascicular spindle cell component. Unequivocal positivity for keratin is a diagnostic requirement for osteoclastoma-like or giant cell-rich carcinoma, with the exception of those cases showing obvious morphologic transition to usual carcinoma.

Prognostic factors

Undifferentiated high grade sarcomas with prominent osteoclastic giant cells behave similarly to other pleomorphic

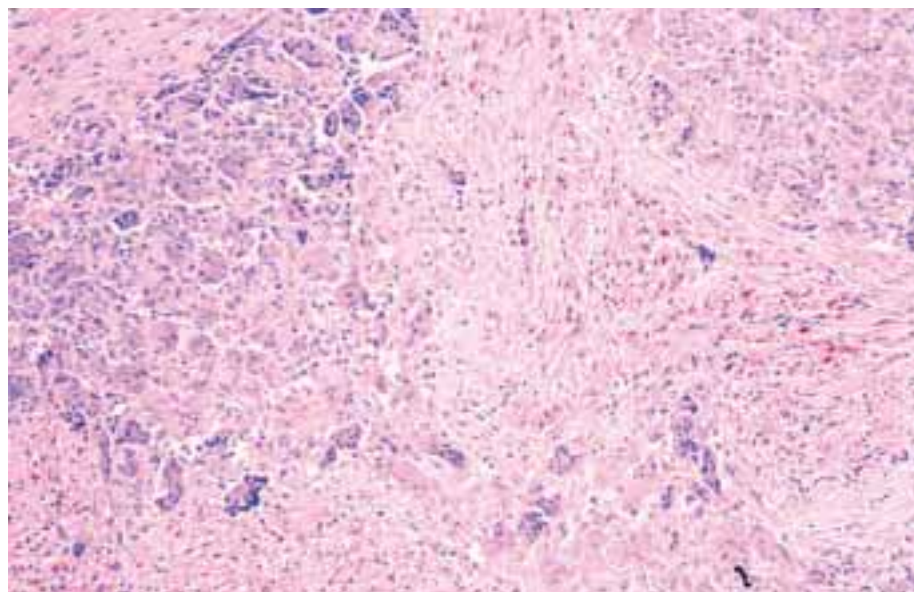


Fig. 3.26 Giant cell MFH may resemble giant cell tumour of soft tissue, which has a multinodular growth pattern, was often formerly labelled as giant cell MFH.

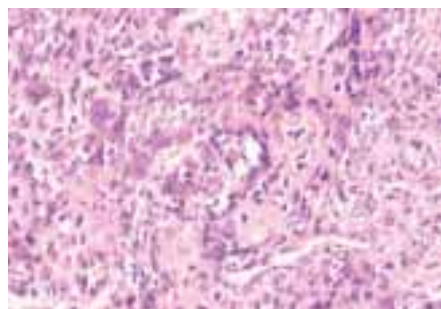


Fig. 3.27 Giant cell-rich soft tissue osteosarcoma. This osteoclast-rich spindle cell malignant neoplasm contains seams of osteoid produced by cytologically malignant cells.

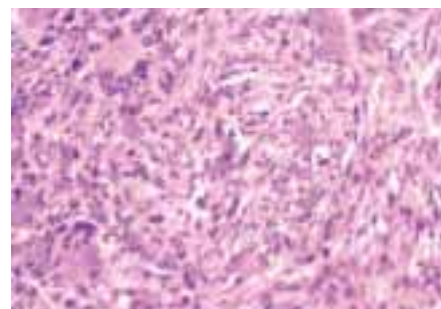


Fig. 3.28 Leiomyosarcoma mimicking so-called giant cell MFH. Note with prominent osteoclastic giant cells and the eosinophilic fascicular spindle cell component.

sarcomas. Among neoplasms simulating giant cell MFH, extraskeletal osteosarcoma and leiomyosarcoma are much more aggressive than giant cell tumour of soft tissues.

Inflammatory malignant fibrous histiocytoma / Undifferentiated pleomorphic sarcoma with prominent inflammation

Definition

A malignant neoplasm characterized by numerous xanthomatous cells, morphologically both benign and malignant, admixed with atypical spindle cells and acute and chronic inflammatory cells. Originally regarded as a variant of so-called malignant fibrous histiocytoma (MFH), differentiation in these tumours is poorly understood and their morphology may be shared by both mesenchymal and epithelial neoplasms. The term inflammatory MFH is now reserved for undifferentiated pleomorphic sarcomas with a prominent histiocytic and inflammatory infiltrate.

ICD-O code 8830/3

Synonyms

Xanthomatous MFH, malignant fibrous xanthoma, xanthosarcoma.

Epidemiology

This is the rarest and the least documented type of MFH, with only two published series of 7 and 8 cases {1096,1198} and a few case reports. There is no apparent gender predominance, and patients are usually more than 40 years old.

Sites of involvement

The most common site is the retroperitoneum but intra-abdominal and deep soft tissue locations have also been observed.

Clinical features

In addition to symptoms and imaging features of a large retroperitoneal tumour, inflammatory MFH may be associated with fever, weight loss, leukocytosis, eosinophilia, and leukaemoid reaction. Analysis of tumour extracts and immunohistochemistry suggested that production of specific cytokines by tumour cells is responsible for the systemic symptoms {1401,2076}.

Aetiology

There is no aetiology known for inflammatory MFH, but one post-radiation case has been reported {735}.

Macroscopy

This tumour is usually large and often displays a yellow colour due to large collections of xanthoma cells.

Histopathology

Inflammatory MFH is characterized by

sheets of benign xanthoma cells with numerous inflammatory cells including neutrophils, eosinophils and a minor component of lymphocytes and plasma cells. Some cases show only a few or no xanthoma cells but are predominantly composed of neutrophils and eosinophils. There are scattered atypical large cells, with one or more irregular, hyperchromatic nuclei with prominent nucleoli. These cells may be rare and difficult to find and occasionally resemble Reed-Sternberg cells. Occasionally atypical cells are xanthomatized and typically display phagocytosis of neutrophils. These cells may be set in a hyalinized collagenous background. In most cases, there are typical areas of pleomorphic MFH-like sarcoma with spindle and pleomorphic cells arranged in a haphazard growth pattern. Like pleomorphic MFH, inflammatory MFH is a diagnosis of exclusion and could represent an inflammatory dedifferentiated component shared by different neoplasms such as carcinomas, lymphomas, leiomyosarcomas, inflammatory myofibroblastic tumours and liposarcomas {956,961}. Among these, dedifferentiated liposarcoma is the most common simulant.

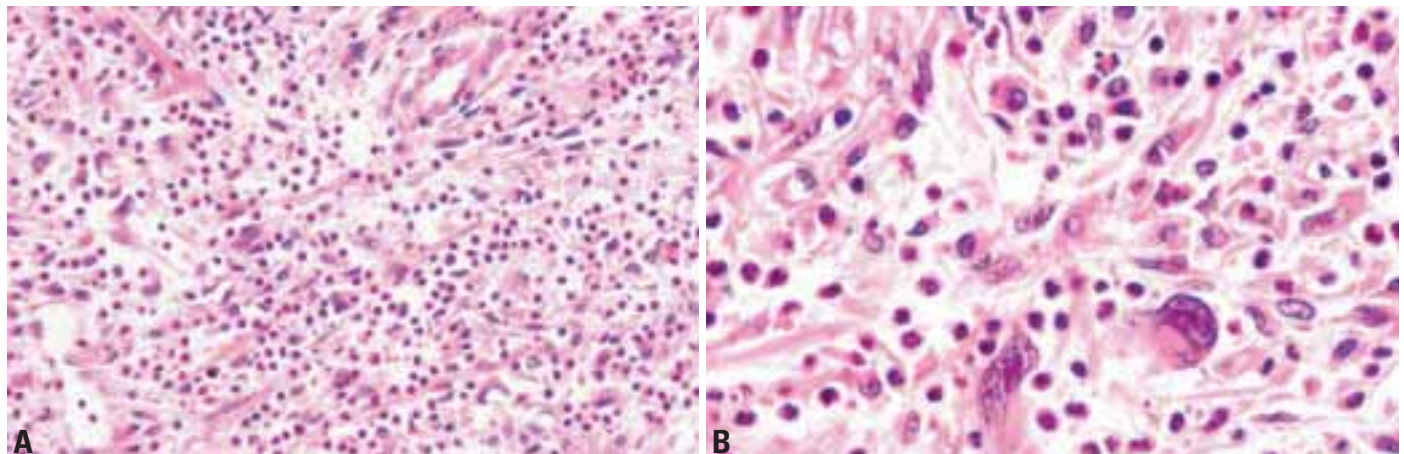


Fig. 3.29 Inflammatory malignant fibrous histiocytoma. **A** Pleomorphic spindle cells are associated with numerous inflammatory cells. **B** The atypical cells may be suggestive of a lymphoid neoplasm.

Therefore inflammatory MFH areas may often be associated with areas of more specific tumours which should be carefully looked for.

Immunophenotype

Immunohistochemistry is useful for showing a specific line of differentiation such as epithelial, lymphoid or smooth muscular. In the other cases, the neoplastic cells express vimentin, occasionally CD68, but are negative for CD15, CD20, CD30, CD43 and CD45 [1096].

Ultrastructure

The tumour cells do not differ ultrastructurally from tumour cells of pleomorphic MFH.

Genetics

Genetic analysis may be particularly useful for identifying a possible dedifferentiated liposarcoma or other simulants such as anaplastic large cell lymphoma.

Prognostic factors

From a review of the literature [961] and a small series [1198], it appears that two-thirds of patients died of their tumour with persistent or recurrent disease. About one fourth of patients developed distant metastasis. As in other retroperitoneal sarcomas, this poor prognosis is probably related to the extent of the tumour and its inaccessibility to proper surgery at the time of the diagnosis.

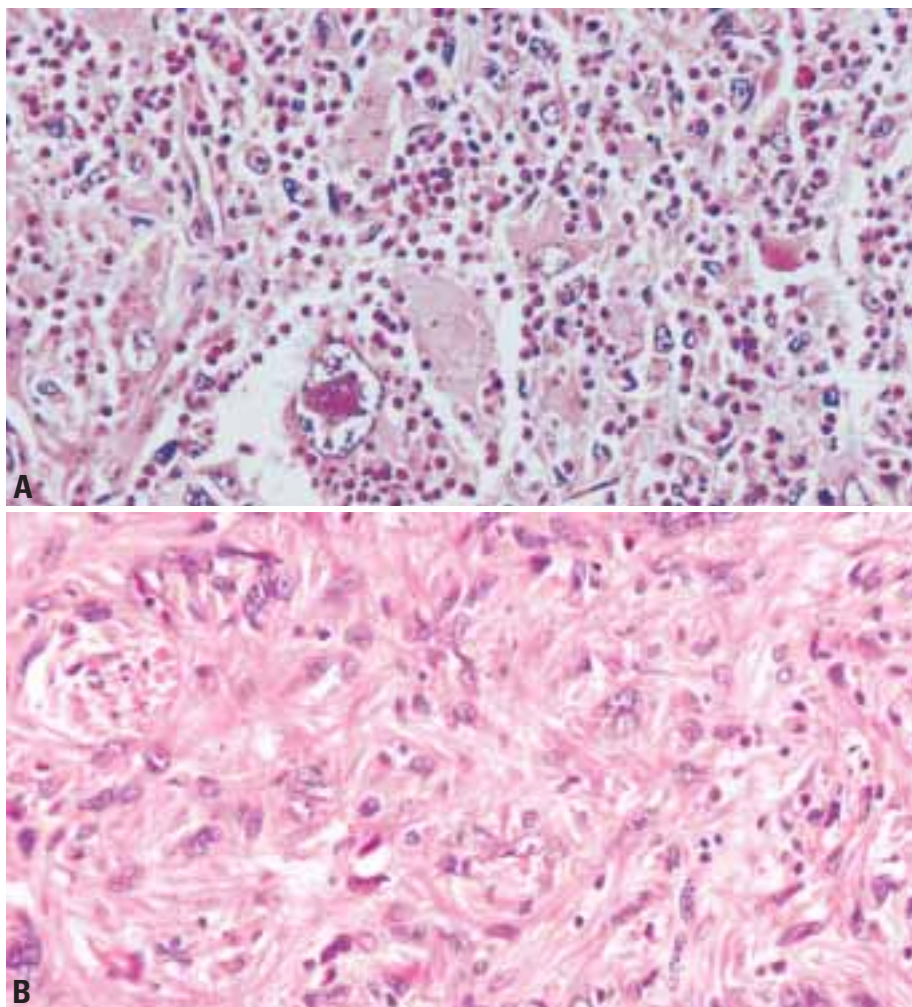


Fig. 3.30 Inflammatory malignant fibrous histiocytoma. **A** Note the striking cytophagocytosis. **B** Pleomorphic MFH-like areas with collagenous stroma are common.