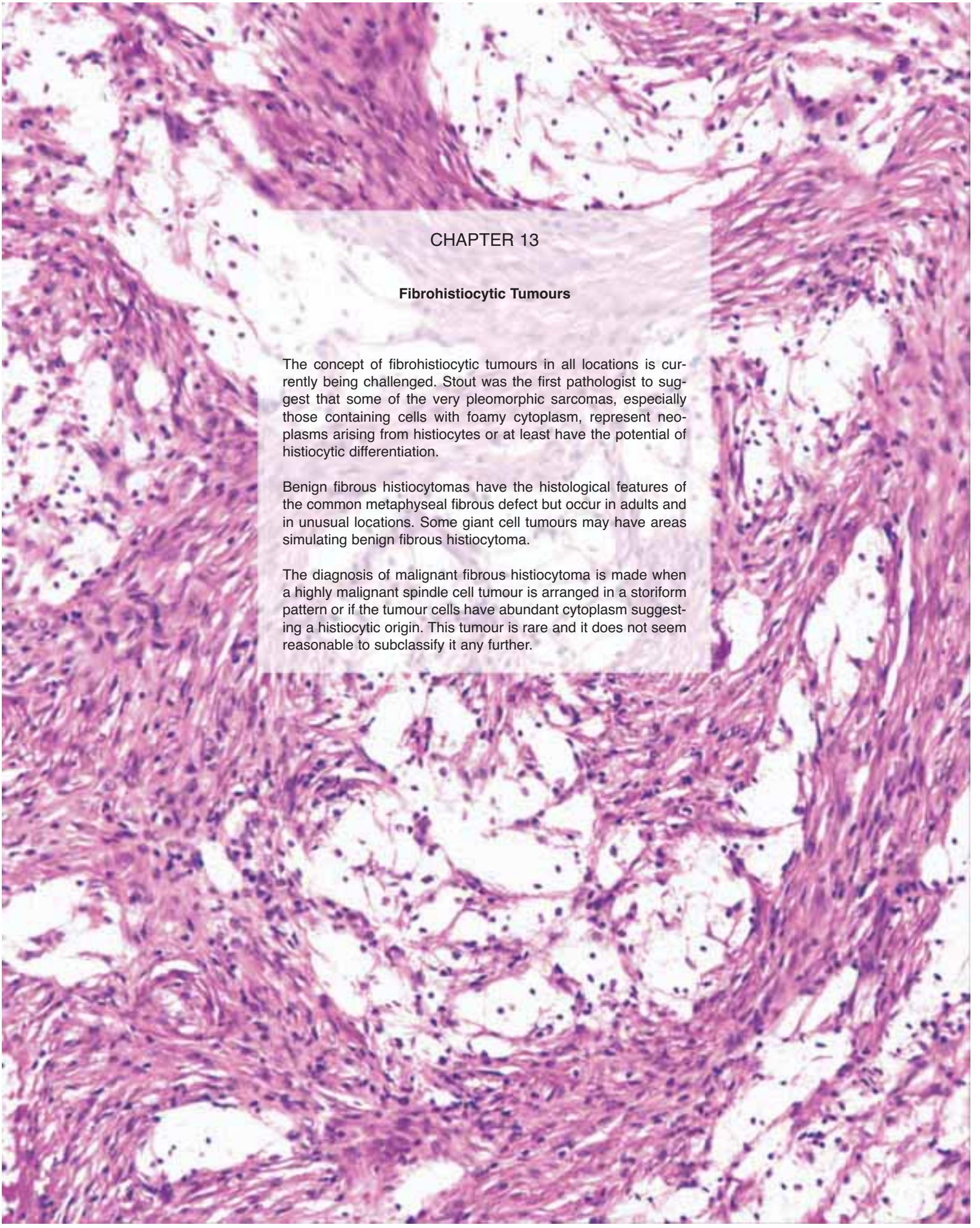

CHAPTER 13

Fibrohistiocytic Tumours

The concept of fibrohistiocytic tumours in all locations is currently being challenged. Stout was the first pathologist to suggest that some of the very pleomorphic sarcomas, especially those containing cells with foamy cytoplasm, represent neoplasms arising from histiocytes or at least have the potential of histiocytic differentiation.

Benign fibrous histiocytomas have the histological features of the common metaphyseal fibrous defect but occur in adults and in unusual locations. Some giant cell tumours may have areas simulating benign fibrous histiocytoma.

The diagnosis of malignant fibrous histiocytoma is made when a highly malignant spindle cell tumour is arranged in a storiform pattern or if the tumour cells have abundant cytoplasm suggesting a histiocytic origin. This tumour is rare and it does not seem reasonable to subclassify it any further.

Benign fibrous histiocytoma of bone

M. Kyriakos

Definition
A benign lesion of bone composed of spindle-shaped fibroblasts, arranged in a storiform pattern, with a variable admixture of small, multinucleated osteoclast-like giant cells. Foamy cells (xanthoma), chronic inflammatory cells, stromal haemorrhages and haemosiderin pigment are also commonly present.

ICD-O code 8830/0

Synonyms
Fibroxanthoma, fibrous xanthoma, xanthofibroma, xanthogranuloma.

Epidemiology
Benign fibrous histiocytoma is rare, with less than 100 reported cases. Patients have ranged in age from 6 to 74 years at diagnosis {110,180}, 60% being older than age 20 years, with a slight female prevalence.

Sites of involvement
Approximately 40% of benign fibrous hisiocytomas occur in the long bones, with femur and tibia most frequently involved. As many as 25% of cases involve the pelvic bones, in particular the ilium. However, this tumour may involve virtually any bone. In the long bones, benign fibrous histiocytoma is centred in the epiphysis or diaphysis.

Clinical features / Imaging
Although some patients (~15%) are asymptomatic {180,583,1639}, in most (65%) the lesion causes pain which may be present for days {877} up to several years {364,1308,1468,1781}. Occasional patients present because of pathological fracture {365,506,939}.
Roentgenographically, benign fibrous histiocytoma (BFH) appears as a well defined, benign appearing, radiolucent medullary defect without matrix formation; internal trabeculation or pseudoseptations, may be evident {365}. Approximately two-thirds of the lesions have sclerotic margins, at times best seen with computed tomography {100, 180,723,877,959}. The lesion may thin and expand the cortex, however, a periosteal reaction is lacking in the absence of fracture {180,364,365,506, 723,765,959,1639,1781,2155}. Soft tissue extension is not present. Rarely, the lesion is less well defined, with indistinct borders, having a pattern suggestive of malignancy {939,2155}. At the end of a long bone it may be central or eccentric and be indistinguishable from a giant cell tumour (GCT) {1355,1875}. The diagnosis of benign fibrous histiocytoma should be considered in cases in which the clinical radiographic setting is also compatible with diagnoses of: metaphyseal fibrous cortical defect, non-ossifying fibroma or giant cell tumour of bone.

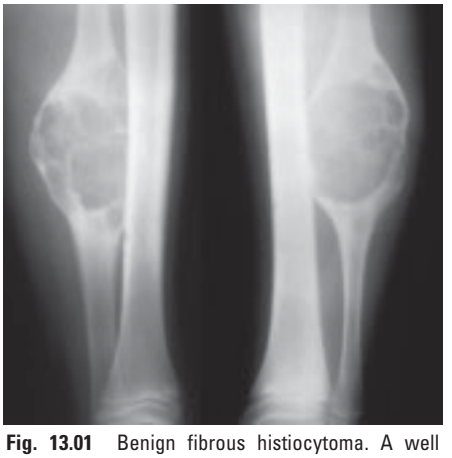

Fig. 13.01 Benign fibrous histiocytoma. A well defined, lytic lesion involves the mid- diaphysis of the fibula in a 10-year- old boy. The lesion expands and scallops the bone.

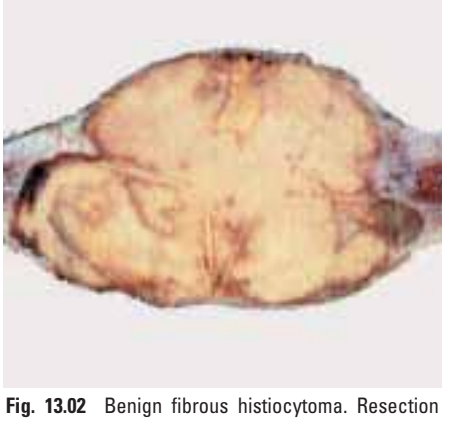

Fig. 13.02 Benign fibrous histiocytoma. Resection specimen of the same lesion (Fig. 13.01) shows a pale, cream-yellow cut surface with focal rust brown areas along its periphery. Marked cortical thinning and endosteal scalloping are evident.

Macroscopy
Most lesions are 3.0 cm in diameter or smaller {100,110,364,583,1308,1484, 1639}, although cases up to 7.0 cm have been reported {723,2155}. The tumour tissue is usually firm, grey-white, and frequently contains irregular yellow to reddish brown foci.

Histopathology
The basic pattern of BFH consists of a stroma of spindle-shaped fibroblasts, arranged, at least focally, in a whorled, storiform pattern, among which a variable number of small, multinucleated, osteoclast-type giant cells are scattered. The spindle cell nuclei may be dark, thin and elongate, or round to oval and vesicular with a micronucleolus. In rare cases the stromal cells exhibit mild nuclear atypia justifying the term "atypical fibrous histiocytoma". There is no consensus as to how extensive or severe the degree of atypia should be to consider a low grade malignancy {1587,1840}. Foam (xanthoma) cells, with small, dark nuclei are frequently, but not always, found interspersed among the stromal cells either individually, or in small clusters or sheet-like masses. Scattered inflammatory cells, mainly lymphocytes, are present, occasionally situated in small, loose clusters. Mitotic figures may be evident but atypical forms are not present. Small stromal haemorrhages are common as are deposits of haemosiderin either as fine cytoplasmic granules within the stromal cells or small macrophages, or as large, extracellular clumps. Zones of ischaemic necrosis may occur secondary to fracture. The lesion is sharply demarcated from the adjacent uninvolved bone, scalloping it without permeation.
BFH must be distinguished from fibrohistiocytic degenerative or repair tissue that

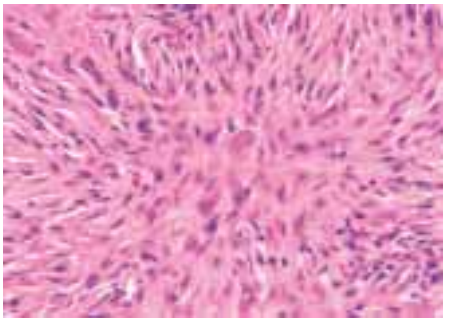

Fig. 13.03 Benign fibrous histiocytoma. Centre of storiform focus shows spindle cells, whose nuclei are elongated or oval with a fine chromatin pattern. Note intracytoplasmic haemosiderin.

occurs in other bone lesions, most notably and frequently in GCT of long bones {180,365,1468}. In an adult with a lytic, destructive lesion at the end of a long bone, careful search for residual foci of GCT must be made before making a diagnosis of BFH {180}.

BFH is histologically indistinguishable from non-ossifying fibroma (NOF), being separated from the latter only on clinical and radiological grounds {1875,2286}, i.e., its location in non-long bones, or lack of metaphyseal involvement if in a long bone; its usual occurrence in older patients; the presence of pain even in the absence of pathological fracture; and a radiological pattern that may lack the well defined, sclerotic, bubble-type margins typical of NOF.

Immunophenotype

There are no specific marker proteins.

Prognostic factors

The prognosis is excellent, surgical curettage / resection usually being curative.

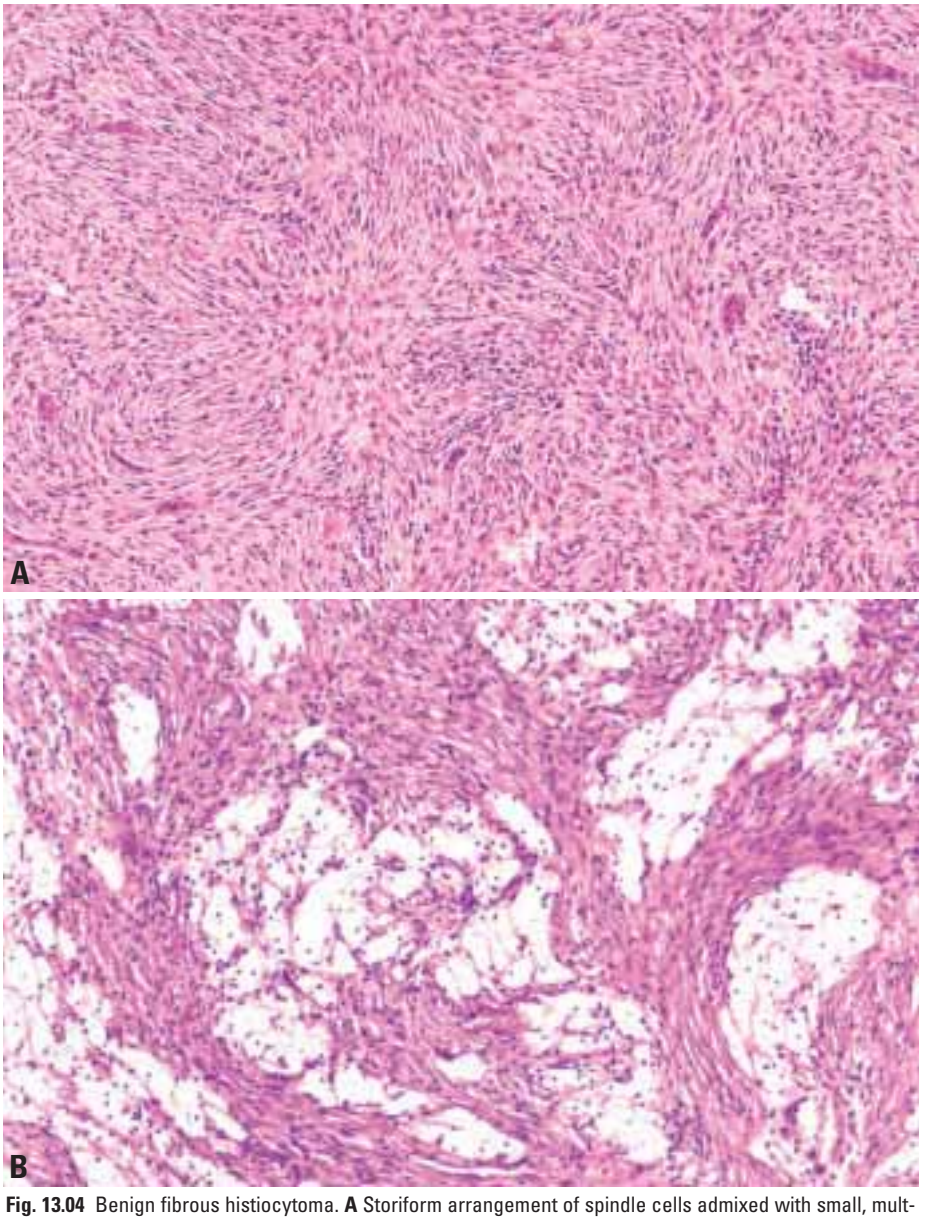

Fig. 13.04 Benign fibrous histiocytoma. **A** Storiform arrangement of spindle cells admixed with small, multinucleated osteoclast-like giant cells. Loose clusters of lymphoid cells are also present. **B** Clusters of foam cells with pale cytoplasm and small, dark nuclei are seen interspersed among whorled spindle cells. Such foam cells may be absent or so extensive as to dominate the lesion.

Malignant fibrous histiocytoma of bone

G.C. Steiner
G. Jundt
J.A. Martignetti

Definition
Malignant fibrous histiocytoma (MFH) defines a malignant neoplasm composed of fibroblasts and pleomorphic cells with a prominent storiform pattern.

ICD-O code 8830/3

Synonyms
MFH was initially described in the bone in 1972 by Feldman and Norman {647}, although similar tumours were earlier described in the soft tissue by Stout and co-workers in 1963 {1632} and 1964 {1589}. MFH has also been termed malignant histiocytoma, xanthosarcoma, malignant fibrous xanthoma and fibroxanthosarcoma.

Epidemiology
Males are more frequently affected than females. MFH of bone is a relatively rare tumour which represents less than 2% of all primary malignant bone lesions. The age of patients at the time of diagnosis is broad and usually varies from the 2nd to 8th decades, with a higher incidence in adults over 40 years of age. Approximately 10-15% of cases occur in patients less than 20 years of age. MFH can arise as a primary bone tumour or may develop secondary to pre-existing bone conditions such as Paget disease or bone infarct, or at the site of bone which was irradiated for the treatment of osseous or extraosseous tumours {503,997,1367}. Secondary MFH accounts for approximately 28% of all MFH {305,538,990, 1571,1648}.

Sites of involvement
Primary MFH predilects the long bones of the lower extremities, particularly the femur (30-45%), followed by tibia and humerus. The knee is a common location, with concurrent involvement of the distal femur and proximal tibia {193}. Among the trunk bones, the pelvis is most frequently involved. Almost all MFH are solitary lesions, but rare multifocal tumours have been reported {1367}.

Clinical features / Imaging
Clinically, most patients complain of pain and, less frequently, swelling that varies from 1 week to 3 years (average 7-9 months). Rarely, a pathological fracture may be the initial presenting symptom.
MFH in the long bones predilects the metaphyseal region with epiphyseal extension in some cases. Diaphyseal location is infrequent. The tumours are essentially osteolytic lesions, but sclerotic areas may be present. The margins are usually ill defined and a moth-eaten or permeative pattern of bone destruction can be observed. Some tumours have well defined borders. The cortex is commonly involved and destroyed by the tumour with often soft tissue extension. Periosteal reaction is not a frequent finding {1272,1522}.

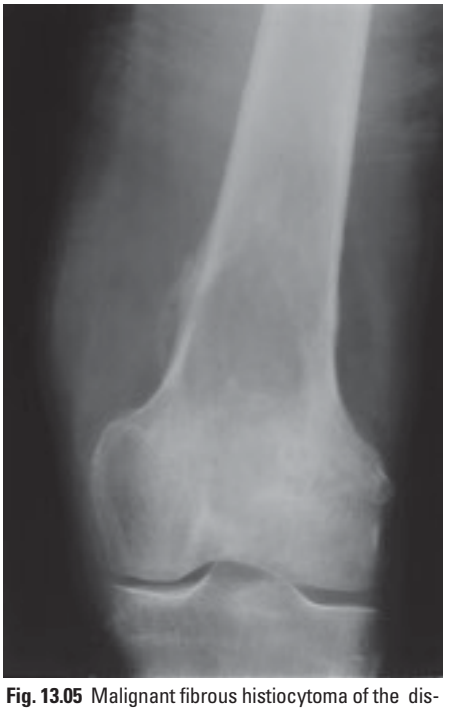

Fig. 13.05 Malignant fibrous histiocytoma of the distal femur, presenting as large, lytic lesion with ill defined margins and focal periosteal reaction.

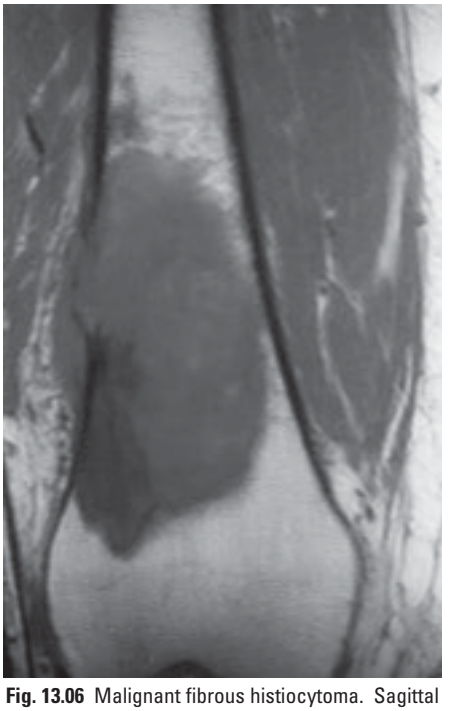

Fig. 13.06 Malignant fibrous histiocytoma. Sagittal T1-weighted MR image showing a large medullary lesion with focal soft tissue extension.

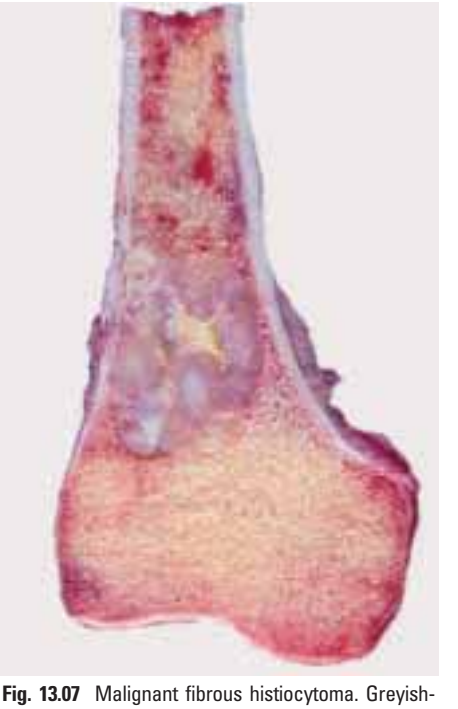

Fig. 13.07 Malignant fibrous histiocytoma. Greyish-white, circumscribed tumour with yellowish necrotic area, focally destroying the cortex (left).

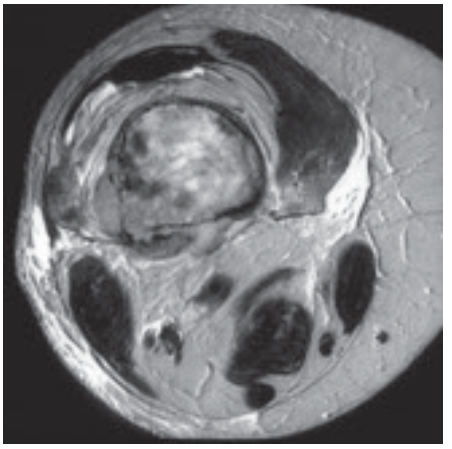

Fig. 13.08 Malignant fibrous histiocytoma of bone. Axial T2-weighted MR image demonstrating an inhomogeneous lesion with cortical destruction and soft tissue extension.

MFH occurring in metaphyseal location can be very aggressive {1522}. The radiographic features of primary MFH are nonspecific and in older patients can mimic lymphoma, myeloma or osteolytic metastases. In younger patients, osteosarcoma and Ewing sarcoma are included in the differential diagnosis. MRI usually helps to demonstrate the intra- and extraosseous extent of the tumour, but the imaging features are not specific to differentiate MFH from other tumours. However, the presence of an eccentric lytic and diaphyseal lesion with cortical destruction and soft tissue extension, or a metaphyseal lytic lesion that extends to the epiphysis but not to the subchondral bone, should raise suspicion of MFH {1272,1522}.

In secondary MFH arising in Paget disease and bone infarct, the radiographs indicate the presence of an underlying bone process in most cases.

Macroscopy

The gross appearance of this tumour is not characteristic. It varies in colour from tan to greyish-white, soft to firm in consistency. Areas of yellowish discolouration, necrosis and haemorrhage are frequently seen. The margins are irregular and often cortical destruction and soft tissue infiltration are present.

Histopathology

Microscopically, MFH consists mainly of a mixed population of spindle cells, histiocytoid and pleomorphic cells. Varying amounts of multinucleated giant cells of the osteoclast type are seen as well as foamy cells and chronic inflammatory cells. The nuclei of the tumour cells may be quite atypical, particularly in the malignant giant cells. Typical and atypical mitoses are present. There is a variability of cellular patterns within these tumours. A characteristic storiform pattern is commonly seen in the fibroblastic areas, in which bundles of spindle cells are arranged in a storiform or pinwheel pattern.

Different histological subtypes have been described in MFH of soft tissue and bone: storiform–pleomorphic, histiocytic, myxoid, giant cell, and inflammatory. The storiform-pleomorphic is the most common histological subtype in bone. The myxoid pattern is rare. Most MFH are high grade tumours, but a few low grade lesions have been reported {305,538, 990,1571,1648}.

Immunophenotype

Immunomarkers are of limited value in the diagnosis of MFH of bone. They are useful to rule out other malignant neoplasms that may resemble MFH such as leiomyosarcomas, metastatic carcinomas and melanomas {675}. Vimentin is strongly positive in tumour cells. Smooth muscle actin, indicative of myofibroblastic differentiation, may be focally positive. The presence of cytokeratin immunoreactivity in MFH is nonspecific. CD68 reactivity may be present in the tumour cells but is not a specific marker for histiocytes and therefore of no diagnostic significance {69,2051}.

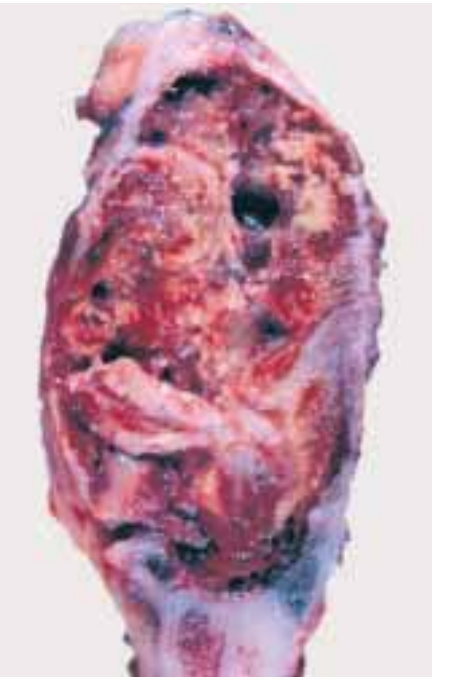

Fig. 13.09 Malignant fibrous histiocytoma of bone. Gross photograph of resected specimen shows yellowish brown, partly cystic tumour tissue.

Differential diagnosis

MFH may have foci of osteoid or primitive bone formation at the periphery of the

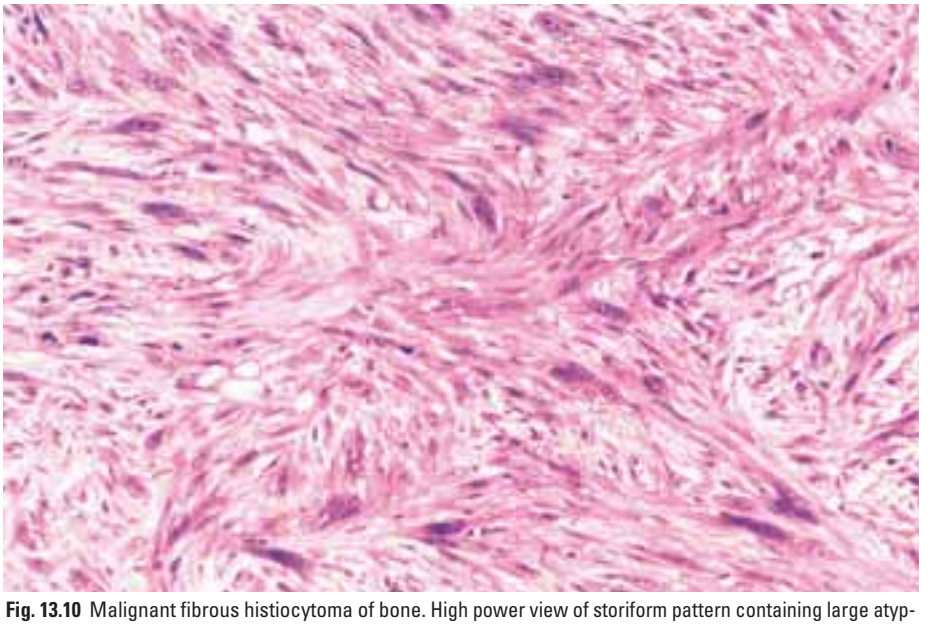

Fig. 13.10 Malignant fibrous histiocytoma of bone. High power view of storiform pattern containing large atypical tumour cells.

tumours in the areas of soft tissue involvement. This usually represents periosteal reactive bone and not osteosarcoma {990}. Also, foci of irregular and coarse collagen fibres within the tumour, which are present in some cases, can be misinterpreted as neoplastic osteoid. In these instances, detailed histological evaluation will help to rule out osteosarcoma, particularly the MFH-like variant of osteosarcoma, which shows unequivocal evidence of mineralised osteoid and bone {1528}. Fibrosarcoma often overlaps histologically, clinically and radiologically with MFH. In contrast to MFH, which contains pleomorphic cells and a storiform pattern, fibrosarcoma consists of bundles of spindle cells with a herringbone pattern {538}. However, histological distinction between one tumour and the other can be arbitrary.

Metastatic carcinoma with a spindle cell component and melanoma should be distinguished from MFH by the use of appropriate immunomarkers.

Genetics

In 5/7 sporadic MFHs, LOH was found for markers within the 9p21-22 region, and the minimally defined region of LOH could be narrowed down even further {1338}. Loss of the 9p21-22 region in bone MFH has previously also been noted using comparative genomic hybridization {1957}. The LOH results are in accord with mutation studies which suggest that *CDKN2A* is not the critical gene {2096}.

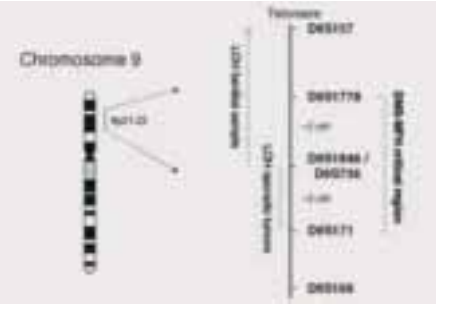

Fig. 13.11 Malignant fibrous histiocytoma of bone. Minimal region of deletion on chromosome arm 9p.

Genetic susceptibility

Diaphyseal medullary stenosis with malignant fibrous histiocytoma (DMS-MFH) is a rare, autosomal dominant bone dysplasia / cancer syndrome of unknown aetiology {85,886}. The skeletal phenotype is characterized by cortical growth abnormalities, including diffuse diaphyseal medullary stenois with overlying endosteal cortical thickening, metaphyseal striations, and scattered infarctions and sclerotic areas throughout the long bones. Notably, malignant transformation has occurred in 13 of 40 patients in the five reported DMS-MFH families {85,886, 1337,1521,1583}. Malignant fibrous histiocytoma has been the consistent diagnosis in all the tumours studied.

Using a positional cloning strategy, the DMS-MFH gene was localized in three unrelated families to chromosome bands 9p21-22 with a maximal two-point LOD score of 5.49 {1337}. Haplotype analysis narrowed the boundaries of the gene locus to an ~3 cM region. These results were independently corroborated in another DMS-MFH family {1521}.

Prognostic factors

MFH is a highly malignant neoplasm with frequent tendency to metastasis, particularly to the lungs (45-50%). The recommended treatment is wide surgical excision. In those patients with histologically high grade and resectable lesions, preoperative chemo therapy appears to be the standard of care. The chemotherapy regimen is similar to that used in osteosarcoma. The degree of tumour necrosis in the resected specimen after chemotherapy is apparently an important prognostic factor, as in the management of osteosarcoma {193,1648}. In patients with localized disease, the 5-year disease-free survival has been reported to be over 50% {246,1648}. Radiotherapy is used particularly in patients with inadequate surgical treatment.

Favourable prognostic factors are: younger age at manifestation (under 40 years); adequate surgical margins and histological low grade. Some authors report that a prominent chronic inflammatory infiltrate is associated with a better prognosis, as opposed to the presence of prominent desmoplasia with hyalinization {2325}. The histological subtype of the lesion does not affect the prognosis.