Malignant fibrous histiocytoma—the commonest soft tissue sarcoma or a nonexistent entity?

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Malignant fibrous histiocytoma (MFH) was first introduced by Ozzelo et al. (1963) and O'Brian and Stout (1964). MFH as a clinicopathological entity was widely accepted when Kempson and Kyriakos (1972) described 30 cases of fibroxanthosarcoma, and their morphologic description was accepted as the prototype for storiform-pleomorphic MFH.

Between 1972–1979 four other variants of MFH were introduced; myxoid, giant cell, inflammatory and angiomatoid and MFH became the commonest of soft tissue sarcomas.

However, despite the fact that MFH was considered and accepted as the most frequent sarcoma, there has been continued discussion over its histogenesis. Several hypotheses have been suggested; true histiocytic origin, fibroblastic origin, dual fibro-histiocytic origin or origin from primitive mesenchymal cells. It has not been possible to prove a definitive histogenesis, ultrastructurally or by immunohistochemistry.

The different subtypes of MFH

Storiform-pleomorphic

This is the most common subtype and most frequently seen as a deep-seated tumour of the extremities in the middle-aged or elderly. It appears commonly as a single, often large mass, frequently with areas of necrosis or haemorrhage. The typical tumour is composed of a mixture of spindle, fibroblast-like cells which are, at least in some areas, arranged in a storiform pattern, together with plump, polygonal or rounded histiocyte-like cells and a variable number of large multinucleated giant tumour cells often with eosinophilic cytoplasm. A typical feature is marked cellular and nuclear pleomorphism and frequent, often atypical mitoses. An admixture of reactive histiocytes and other inflammatory cells is common. There is no specific vascular architecture and no specific immunophenotype. The most typical ultrastructural findings are the presence of fibroblast- and histiocyte-like cells and myofibroblast-like cells. The 5-year survival rate is reported to be 30–40%.

Myxoid

Myxoid MFH is the next common subtype. The patients are often elderly and the most frequent site is in the subcutaneous tissue of extremities (60%). The proportion of myxoid areas required for the diagnosis varies between different investigators from 10–50% of the tumour mass. In the low grade malignant tumours there is a prominent myxoid matrix containing a typical vascular architecture; numerous, elongated, curved, thin-walled vessels. In the low grade tumours there is a predominance of more or less atypical spindle or stellate cells. High grade tumours resemble storiform-pleomorphic MFH. This subtype has been thoroughly investigated by Angervall et al. (1977) and Merck et al. (1983) and the name myxofibrosarcoma was suggested. In common with the storiform-pleomorphic type the myxoid MFH does not display a histiocytic immunophenotype, vimentin-positivity is seen in all cases and some cells may express smooth muscle or muscle specific actin. At electron microscopic examination, most cells show fibroblastic differentiation. The metastatic potential is related to grade, low grade tumours rarely metastazise.

Giant cell

A rare variety, only about 10% of MFH are considered to belong to this type. It is predominantly a superficial multi-nodular tumour composed of pleomorphic, polygonal cells often with eosinophilic cytoplasm. Fascicles of spindly, fibroblast-like cells are found as well as pleomorphic tumour giant cells. The typical finding is the presence of numerous large multinucleated osteoclast-like cells with benign looking nuclei. Small foci of osteoid or bone have been described. Some cases have been shown to express muscle specific actin and desmin at immunohistochemistry and the osteoclast-like cells display a histiocytic phenotype. The deep-seated tumours are as aggressive as storiform-pleomorphic MFH while superficial tumours are less aggressive.

Inflammatory

This is the rarest type and the least documented. The most common site is the retroperitoneum and constitutional symptoms such as fever and leukocytosis are not uncommon. Macroscopically the tumour surface is often yellow or yellow-brown due to large collections of xanthoma cells. Besides these cells the tumour is composed of large atypical cells with irregular nuclei with prominent nucleoli and a heavy mixture of inflammatory cells, mostly neutrophils. Little is known about the immunohistochemical phenotype and ultrastructure. This subtype is reported to have a poor prognosis.

Angiomatoid

This was the last subtype to be described. It occurs predominantly in children and young adults. The typical tumour is a slowly growing nodular subcutaneous mass on the extremities. Some cases are associated with systemic symptoms such as anemia and night sweats. Angiomatoid MFH is a nodular tumour surrounded by a pseudocapsule and composed of oval, rounded or spindle cells with bland nuclei with a slight pleomorphism. The cells are arranged in sheets or whorls. Within the nodules there are irregularly shaped blood-filled spaces, often lined by tumour cells, sometimes by endothelium. Hemorrhage and hemosiderin deposits are common. An inflammatory infiltrate often surrounds the tumour nodules. Immunochemical as well as ultrastructural studies have produced conflicting and different results. Histiocytic as well as myogenic differentiation have been suggested and some researchers reported desmin positivity in tha majority of investigated cases. The prognosis is good, only 5% metastasizing.

Reappraisal of MHF

During the years, confusing information regarding MFH has emerged. More than 30 different entities of sarcomas have been described but one type (MFH) is diagnosed in 25–40% of cases. These differences in frequency might be related to poor diagnostic reprodicibility among histopathologists. Furthermore a specific histogenesis has never been proved and there is obvious clinical and morphological heterogeneity between the different subtypes.

These conflicting data has led some histopathologists to suggest that MFH, or at least the storiform-pleomorphic subtype, could represent a common morphologic appearance of a number of poorly differentiated sarcomas and, rarely, other malignancies. These ideas have been proposed by Snover et al. (1982), Dehner (1988) and Brooks (1986) and the hypothesis was based on cases showing areas of well-differentiated sarcoma entities within the undifferentiated pleomorphic MFH. Brooks suggested that MFH could represent a final common pathway of tumour progression.

Table 1. The final diagnosis after re-evaluation of 140 pleomorphic sarcomas (19 surgical biopsy specimens omitted; Fletcher 1992)

	n	%
Not sarcoma	20	12
Liposarcoma	40	25
Leiomyosarcoma	29	18
Rhabdomyosarcoma	10	6
Malignant mesenchymoma	7	4
Extraskeletal osteosarcoma	6	3
MPNST	5	3
Pleomorphic sarcoma, not classifiable. MFH?	42	26

MPNST, malignant peripheral nerve sheath tumour

The first soft tissue tumour pathologist who energetically and critically reapprasied storiform-pleomorphic MFH was Fletcher. In 1992 he published a thorough re-examination of 159 tumours, primarily diagnosed as pleomorphic sarcomas, of them 101 had been diagnosed after 1973 and half of those as storiform-pleomorphic MFH (Fletcher 1992).

In all these tumours blocks were recut and the tumours were examined with routine stains, immunohistochemistry and electron microscopy in those 18 cases where tissue fixed in glutaraldehyde was available. Diagnostic criteria for different sarcoma histotypes such as liposarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumour, malignant mesenchymoma, extraskeletal osteosarcoma as well as for pleomorphic non-sarcomatous malignancies were defined and strictly followed in the re-evaluation. (Table 1).

The relatively high number of non-sarcomatous tumours found (12%) may be explained by the fact that many of those were diagnosed before immunohistochemistry became a routine diagnostic procedure.

Fletcher claimed that he could find a specific line of differentiation in about 75% of these pleomorphic neoplasms and by exclusion only 42 out of the 159 were finally diagnosed as pleomorphic sarcoma, possibly MFH. In another publication the various subtypes of MFH were reappraised and with the following conclusion (Hollowood and Fletcher 1995).

Storiform-pleomorphic MFH. This diagnosis is one of exclusion and they regard this subtype to represent a morphologic manifestation of progression shared by a wide variety of sarcomas and some other neoplasms. When any line of differentiation can be

proved it is sufficient to diagnose the tumour in question as a poorly differentiated example of a specific histotype.

Myxoid MFH is regarded as a specific clinicopathologic entity as the low grade as well as the high grade tumours display a homogeneity but they propose that the name is changed to myxofibrosarcoma.

Giant cell MFH. They propose the same argument as for storiform-pleomorphic MFH and consider that the largest subset of giant cell MFH is an osteoclast-like variant of extraskeletal osteosarcoma followed by poorly differentiated leiomyosarcoma.

Inflammatory MFH also represents the same morphologic pattern of dedifferentiated neoplasms as the storiform-pleomorphic and giant cell types. Due to its rarity there is at present no critical analysis of this histotype.Tumour types diagnosed as inflammatory MFH include Hodgkin's disease, T-cell non-Hodgkin's lymphoma, a variety of epithelial neoplasms and myogenic sarcomas.

Angiomatoid MFH is clinically as well as morphologically different from the other subtypes and is considered to represent a distinct entity in which a substantial number of tumours show myogenic or myofibroblastic differentiation.

Recently Schürch et al. (1996) studied 64 pleomorphic sarcoma of which they diagnosed 24 as consistent with storiform-pleomorphic MFH but as many as 32 were diagnosed as myogenic (18 pleomorphic rhabdomyosarcoma and 14 pleomorphic leiomyosarcoma, respectively). They concluded that these sarcoma, irrespective of type, often looked morphologically alike at histological examination and an accurate diagnosis demanded ancillary techniques, especially immunohistochemistry and electron microscopy.

It is of interest to note that 18/64 were diagnosed as pleomorphic rhabdomyosarcoma. Before the era of MFH, pleomorphic rhabdomyosarcoma was an accepted entity but thereafter considered a rare or non-existent tumour. With the MFH-concept critically re-evaluated, pleomorphic rhabdomyosarcoma has returned as an example of pleomorphic sarcoma with a definable line of differentiation.

The present opinion of MFH

In the latest edition of the standard work *Soft tissue tumors* (Enzinger and Weiss 1995) there is a detailed description of the different MFH-subtypes with the exception of the angiomatoid type which is regarded as a specific entity, a tumour of fibroblastic origin.

In the discussion, however, it is stated that there has been a change in the view of MFH since the term was introduced, especially on the storiform-pleomorphic type. A histiocytic differentiation is no longer accepted but fibroblastic differentiation is suggested. The hypothesis of Fletcher that it is possible to find a specific line of differentiation (myogenic, lipogenic etc) through thorough investigation, including supplementary diagnostic methods, is accepted. Enzinger and Weiss consider that the diagnosis of storiform-pleomorphic MFH rests on the absence of lines of differentiation and they conclude their discussion thus: "The diagnosis continues to serve a useful purpose in identifying an undifferentiated pleomorphic sarcoma although in time it may be more intellectually fortright to consider a change in nomenclature".

In the second edition of *Histologic typing of soft tissue tumors* in the series International histological classification of tumors of the Word Health Organization published 1994, MFH is categorized as a fibrohistiocytic tumor and all subtypes except the angiomatoid are listed.

Reappraisal of MHF in the Musculoskeletal Tumor Centre, Lund

In an ongoing collaborative study with Fletcher 100 soft tissue sarcoma, primarily diagnosed as MFH (all types) 1980–1996 have been re-examined. Only cases with primary, definitive surgery in Lund with all paraffin blocks available were chosen. These cases were investigated according to the same protocoll devised for the re-evaluation of the 159 pleomorphic sarcomas 1992 (Fletcher 1992). The reevaluation diagnoses are tabulated in Table 2 (unpublished data).

Peer review of MFH registered in the Scandinavian Sarcoma Group from 1986 onwards

The Scandinavian Sarcoma Group (SSG), is a multidisciplinary, cooperative association of specialists from the Nordic Countries. From 1986 and onwards all soft tissue sarcoma and bone sarcoma diagnosed in the participating institutions have been registered in a data base (the SSG Central Registry). In 1995 it was decided that a peer-review of registered soft tissue sarcoma should start. In March 1996, 2126 sarcoma had been registered, of them 698 MFH (33%).

Hitherto 255 MFH have been re-examined (re-examination of available material, no recutting of blocks or supplementary investigations). 82 tumours have been excluded as not beeing compatible with MFH and in 16 cases the MFH-diagnosis was seriously questioned. Thus, in 98/255 (38%) the diagnosis of MFH was altered or in doubt (unpublished data).

Based on these studies it is apparent that a specific line of differentiation (lipogenic, myogenic, Schwann cell or non-sarcomatous) is possible to ascertain in a

Table 2. Final diagnosis after re-evaluation of 100 tumours primarily diagnosed as MFH (all types) 1980–1996 at the Musculoskeletal Tumor Centre, Lund University Hospital

Myxofibrosarcoma		*31*
Myogenic sarcoma		*30*
Leiomyosarcoma	20	
Pleomorphic rhabdomyosarcoma	1	
Myogenic sarcoma NOS	2	
Suggested myogenic sarcoma	7	
Liposarcoma		*5*
Pleomorphic	3	
Dedifferentiated	1	
Low grade	1	
Myofibroblastic sarcoma		*9*
Myofibroblastic sarcoma	2	
Suggested myofibroblastic sarcoma	7	
MPNST		*2*
Malignant mesenchymoma		*2*
Soft tissue osteosarcoma		*2*
DFSP with fibrosarcomatous areas		*1*
Low grade fibromyxoid sarcoma		*1*
Sarcoma NOS		*15*
Pleomorphic	11	
Spindle	2	
Pleomorphic/myxoid	1	
Spindle/myxoid	1	
Nodular fasciitis		*1*
Metastatic sarcomatoid carcinoma?		*1*

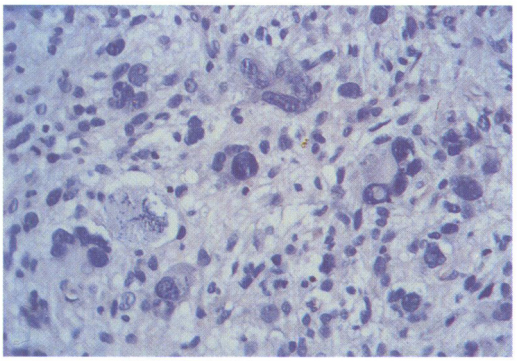
MPNST, malignant peripheral nerve sheath tumour
DFSP, dermatofibromosarcoma protuberans

Table 3. Follow up (4–154 months) of 32 of 100 tumours primarily diagnosed as MFH (all types) 1980–1996 at the Musculoskeletal Tumor Centre, Lund University Hospital with metastases

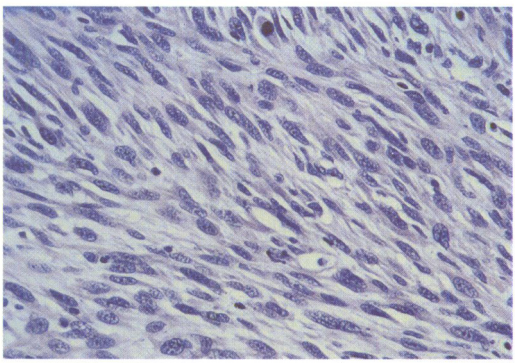
Re-examination diagnosis	Total material	Metastasis	Median time[a]
Myxofibrosarcoma	31	6	20
Myogenic sarcoma	30	16	9
Myofibroblastic sarcoma	9	4	11
Pleomorphic liposarcoma	3	2	15
Spindle cell sarcoma	2	1	12
Soft tissue osteosarcoma	2	1	8
Pleomorphic sarcoma	11	1	26

[a]Median time from surgery to first metastasis (months)

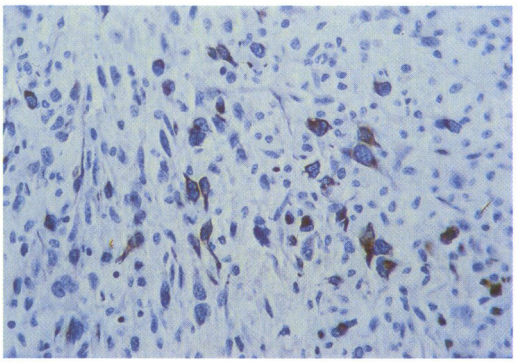
Figure 1. Sarcoma with myogenic differentiation (leiomyosarcoma).



A. Pleomorphic area with numerous bizarre tumour cells. HE, ×100.



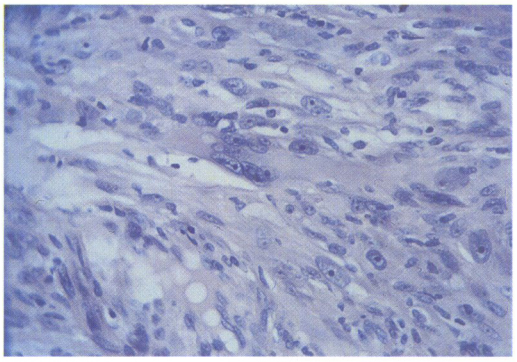
B. Area with fascicles of spindle cells with atypical, often blunt-ended nuclei. HE, ×100.



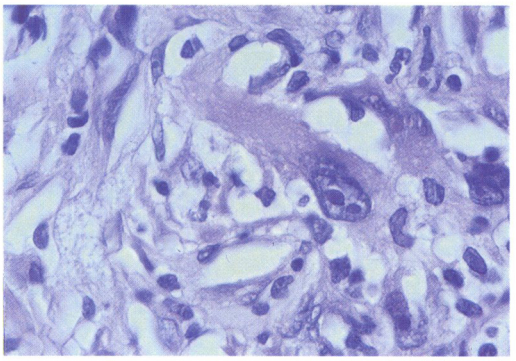
C. Positive immunohistochemical staining of tumour cells for desmin, ×100.

high number of pleomorphic sarcoma initially diagnosed as MFH, especially the storiform-pleomorphic variety (Figures 1–4). Whether this hunt for a specific line of differentiation, although in only small foci of large pleomorphic sarcoma is of clinical (prognostic) importance is still unknown. In the clinical follow up of the 100 Lund-MFH re-examined by Fletcher 32 of the 100 patients had developed metastases during the follow up time (in October 1996, 4–154 months). In 30 of the 100 MFH:s the definitive or suggested re-evaluation diagnosis was myogenic sarcoma (Table 2) and 16 of the 32 metastazing sarcomas were of myogenic origin. Thus more than half of the myogenic sarcoma developed metastases during the follow up

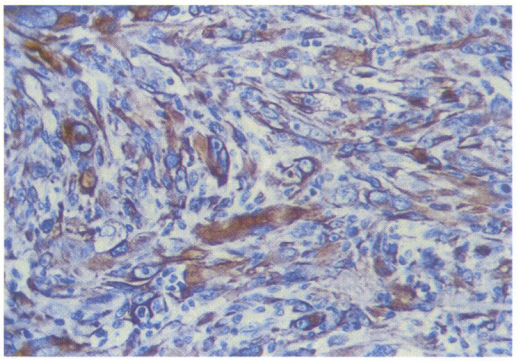
Figure 2. Pleomorphic sarcoma with myogenic differentiation (pleomorphic rhabdomyosarcoma).



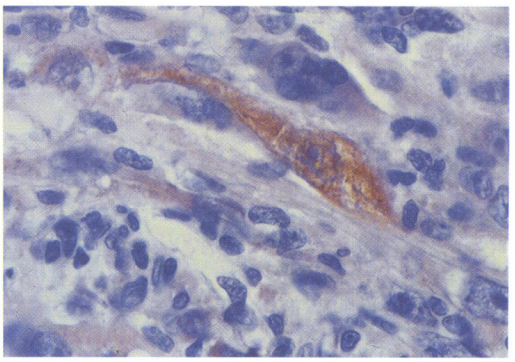
A. Strap-shaped rhabdomyoblast like cells with abundant eosinophilic cytoplasm. HE, ×100.



B. ×250.



C. Positive immunohistochemical staining of tumour cells for desmin, ×100



D. Positive immunohistochemical staining of scattered strapshaped, myoblast-like cells for myoglobin, ×250.

and the median time from surgery to the diagnosis of the first metastasis was 9 months.

In the next common rewiew diagnosis, myxofibrosarcoma, 6 out of 31 developed metastasis with a medeian time of 20 months.

The pleomorphic sarcomas with a myogenic differentiation were the most aggressive in this material (Table 3).

Further studies are necessary to investigate whether a thorough search for differentiation in pleomorphic sarcomas commonly diagnosed as MFH, especially the storiform-pleomorphic type is clinically important. However, it is necessary that guidelines, which are reproducible and accepted for the search for lines of differentiation, are drawn up.

Conclusions

A specific line of differentiation can be discerned in the majority of MFH, especially the storiform-pleomorphic type. Myxoid MFH is a specific entity but the term myxofibrosarcoma is a better name for this type. Angiomatoid MFH is a specific entity. Pleomorphic rhabdomyosarcoma is a specific entity among the pleomorphic sarcomas.

The term storiform-pleomorphic MFH should be reserved for those pleomorphic sarcoma where a specific line of differentiation is not clear. It is recommended that these sarcomas are reclassified to pleomorphic sarcoma without any evidence of differentiation.

Malignant fibrous histiocytoma has probably ceased to be the most frequent sarcoma, but it is at present not possible to decide whether it is a nonexistent entity.

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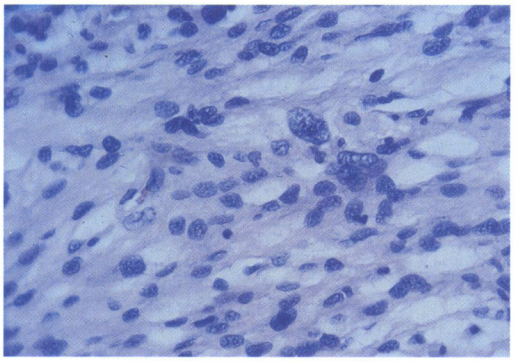
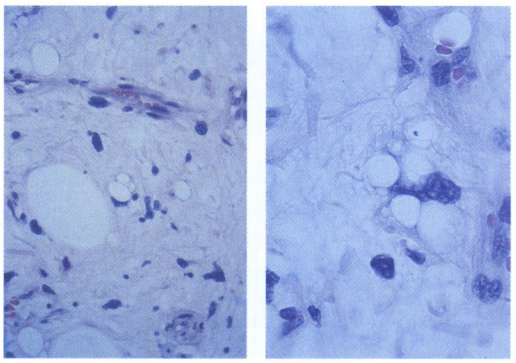
Figure 3. Sarcoma with lipogenic differentiation (pleomorphic liposarcoma).

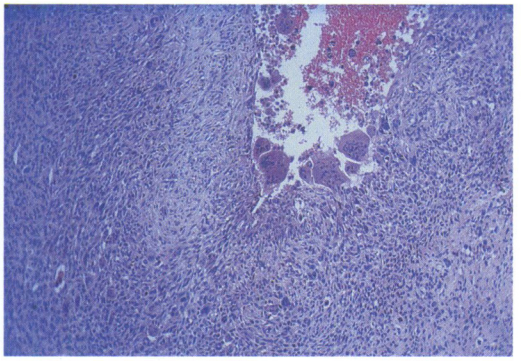


A. Pleomorphic area with numerous bizarre tumour cells. HE, ×100.

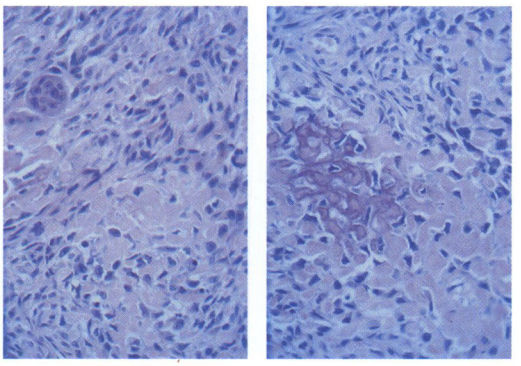


B. Another area with two multivacuolated, atypical lipoblasts. HE, ×100.

Figure 4. Soft tissue osteosarcoma.



A. Pleomorphic sarcoma with osteoclast like giant cells. HE, ×100.



B. Strands of calcified osteoid bordered by tumour cells. Arrow osteoclast like giant cell. HE, ×100.

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