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REVIEW ARTICLE

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Malignant fibrous histiocytoma: past, present, and future

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Introduction

Few tumors have generated more controversy during the past several decades than malignant fibrous histiocytoma (MFH). To those at the periphery of the debate, MFH represents a common, aggressive, soft tissue sarcoma of adulthood. However, to those embroiled, MFH is either a wastebasket term for poorly differentiated sarcomas of a variety of different phenotypes, or a distinct clinicopathologic entity, albeit one having a misleading name. As a spark quickly becomes a flame, then grows into a roaring fire, only to diminish into a smoldering ember, so too has MFH run its nosological course. The widespread recognition and popularity that soon followed its initial description has dwindled over the past decade as the entity MFH has fallen into disrepute.

The past

Information derived from histologic and cell culture studies provided the foundation for the concept of MFH in the United States. It was during the first half of the twentieth century that neoplasms with histiocytic features were originally described and designated 'histiocytomas' and 'xanthomas' and related tumors with fibroblastic components were considered 'fibroxanthomas' [1, 2, 3]. Tumor classification during that time period was based on the concept of histogenesis or 'cell of origin' [4]. The histologic resemblance of neoplastic cells and the characteristics they exhibited in culture relative to normal cell or tissue types defined the cell of origin. The histogeneses of 'histiocytoma', 'xanthoma', and 'fibroxanthoma' were somewhat contentious, as proponents supported histiocytic, fibroblastic, or other speculative origins for these tumors. Cultured explants of benign and malignant variants of these neoplasms showed that during the first several days of growth, the tumor cells exhibited some of the characteristics of histiocytes in that they developed several short cytoplasmic processes, moved in an ameboid fashion, and contained abundant granular cytoplasm [4, 5, 6]. As the cells aged in culture, they acquired some of the qualities of fibroblasts becoming progressively more elongate, slender, and bipolar. Both cell types were phagocytic and readily ingested particles of lithium carmine. Not surprisingly, these neoplastic cells were interpreted as being histiocytic in origin, yet capable of developing the structural and functional characteristics of fibroblasts (facultative fibroblasts) [5]. This hypothesis of histiocyte plasticity became the framework of the concept of fibrohistiocytic neoplasms in the early 1960s and was espoused by Stout, who later became known as the father of American soft tissue pathology [7]. Soon thereafter, in the late 1960s and early 1970s, the term malignant fibrous histiocytoma was coined, popularized, and formally incorporated into classification schemes and routine diagnostic nomenclature [8, 9, 10, 11, 12].

Histologically, MFH became the stereotypic pleomorphic sarcoma. It was composed of severely atypical spindle cells (fibroblastic component) arranged in a storiform pattern, admixed with numerous large bizarre polyhedral cells (histiocytic component). Mitoses including struc-

Table 1 Previous and proposed reclassification of MFH

Previous classification of MFH	Proposed reclassification of MFH
Storiform-pleomorphic MFH	Storiform-pleomorphic Fibrosarcoma
Myxoid MFH	Myxofibrosarcoma
Inflammatory MFH	Inflammatory pleomorphic Fibrosarcoma
Giant cell rich MFH	Giant cell rich Fibrosarcoma
Angiomatoid MFH	Angiomatoid fibrohistiocytic tumor

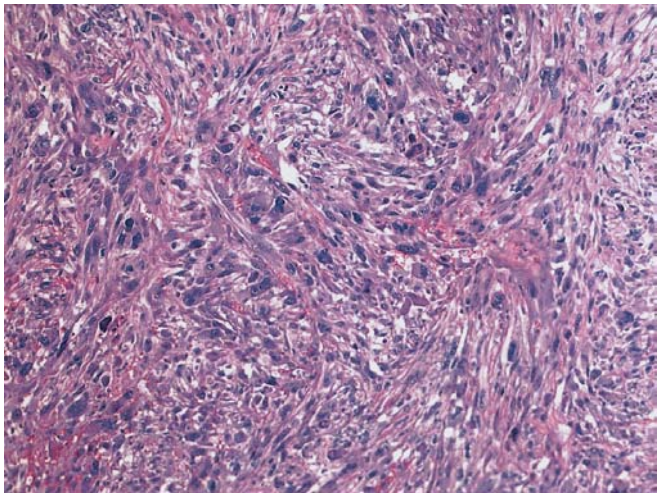

Fig. 1 Storifom-pleomorphic MFH composed of fascicles of severely atypical spindle cells arranged in a whorling or storiform pattern

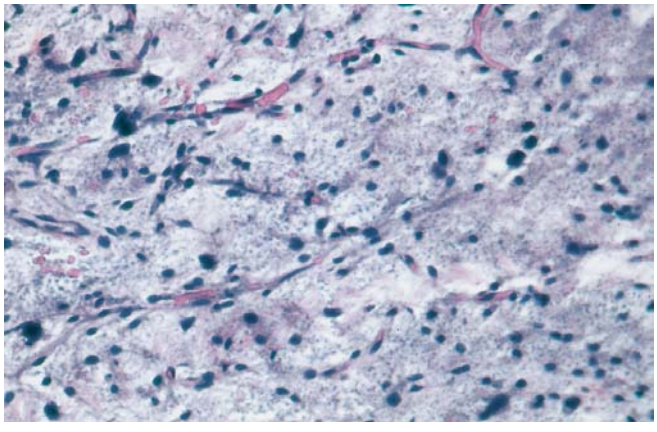

Fig. 2 Atypical spindle cells enmeshed in a myxoid stroma containing delicate branching capillaries characteristic of myxoid MFH

turally abnormal forms were frequent and necrosis and hemorrhage were commonplace and often extensive. The first electron microscopic studies of these tumors in the 1970s showed that the neoplastic cells had ultrastructural features associated with fibroblasts and that some of the

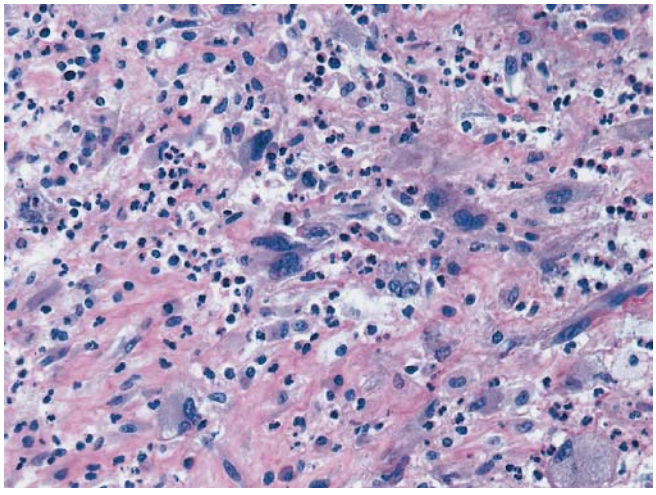

Fig. 3 Malignant spindle and polyhedral cells surrounded by prominent inflammatory infiltrate are typical of inflammatory MFH

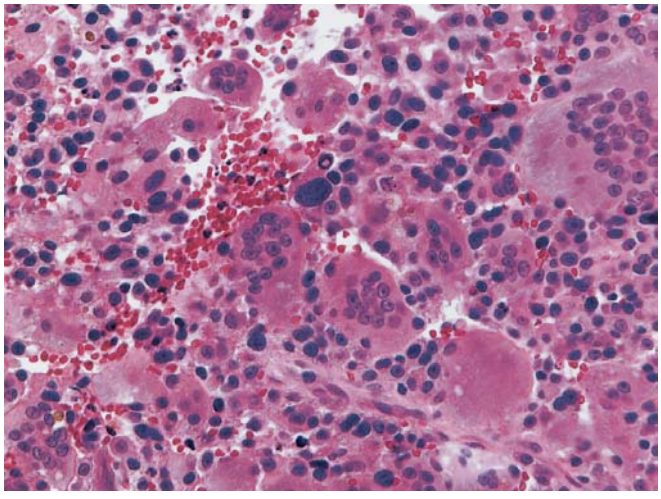

Fig. 4 Atypical spindle cell enmeshed in a myxoid stroma containing delicate branching capillaries characteristic of myxoid MFH

cells also contained lysosomes, an organelle characteristic of but not specific for histiocytes, and this seemingly supported Stout's concept [13, 14, 15].

As experience with MFH accumulated, several subtypes including the storiform-pleomorphic, myxoid, inflammatory, giant cell rich and angiomatoid variants were defined (Table 1) (Figs. 1, 2, 3, 4, and 5) [16, 17, 18, 19]. Previously, these tumors had been classified as other nosologic entities such as fibrosarcoma, pleomorphic rhabdomyosarcoma, pleomorphic liposarcoma, and sarcomatoid carcinoma [20]. By 1980, hundreds of cases of MFH had been reported and their clinical characteristics had become well recognized. With the exception of the angiomatoid variant, these tumors usually occurred in middle-aged adults or the elderly and were large, high

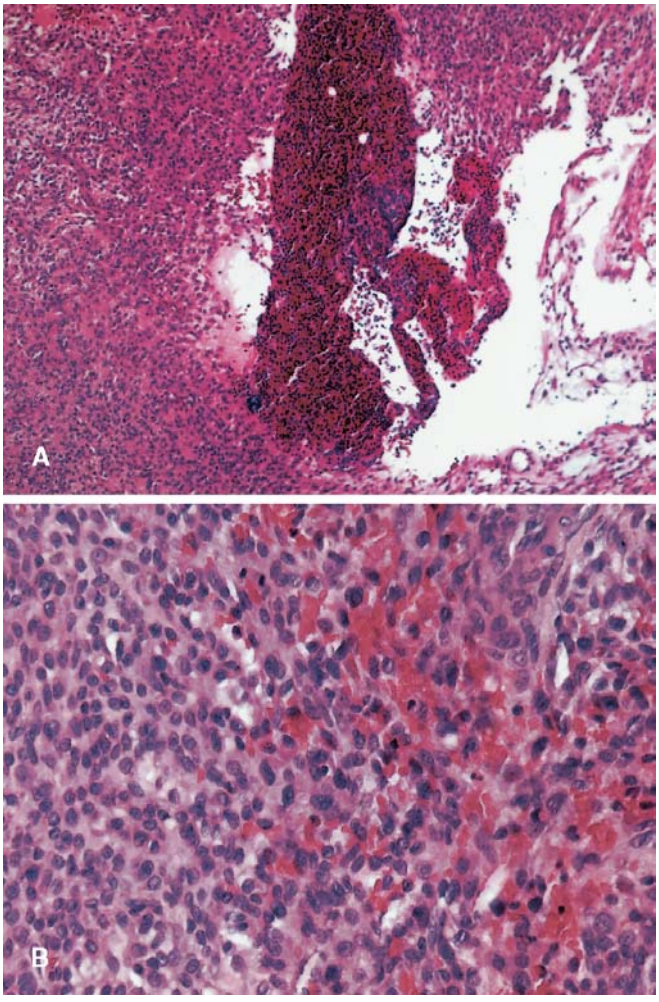

Fig. 5 **A** Central portion of angiomatoid fibrohistiocytic tumor containing blood filled cystic space surrounded by tumor cells. **B** Bland spindled tumor cells with admixed blood

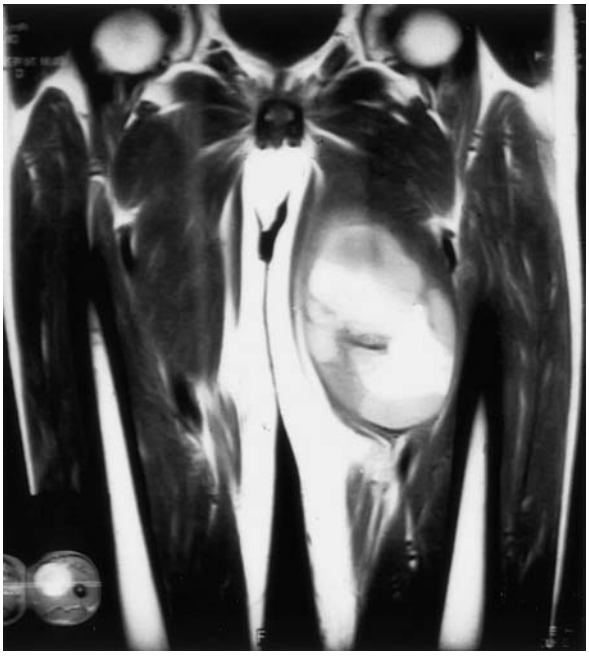

Fig. 6 Coronal T1 weighted MRI demonstrating a large, deep-seated, heterogeneous mass (MFH) in the thigh. The high signal intensity represents intratumoral hemorrhage

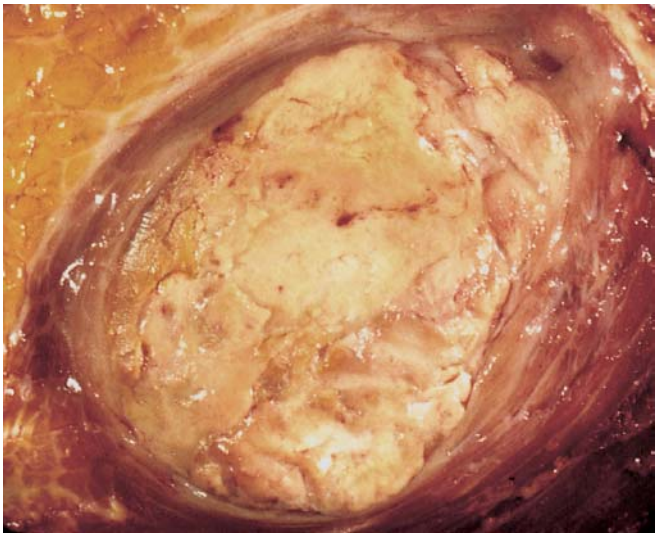

Fig. 7 MFH within skeletal muscle and adjacent to subcutaneous fat. The tumor has a pale tan cut surface with scattered glistening mucinous and hemorrhagic areas. The tan regions contain the storiform-pleomorphic component, whereas the glistening mucinous regions are morphologically myxoid and foci of hemorrhage denote tumor necrosis. The pseudocapsule causes the tumor to have deceptively well-circumscribed margins

grade, and biologically aggressive. They frequently originated in the musculature of the proximal extremities and retroperitoneum; however, they could be found anywhere in the body, including the superficial soft tissues, viscera, and the skeleton (Figs. 6 and 7) [21, 22, 23]. Most MFHs arose de novo; however, a minority developed as a long-term sequela of radiation [24].

In the 1980s, MFH, especially the storiform-pleomorphic and myxoid variants (Figs. 1 and 2), became recognized as the most common soft tissue sarcoma of adulthood. Analyses of large numbers of cases identified important prognostic features; older patient age, proximal and deep location, size greater than 5 cm, high histologic grade, and the presence of metastases at the time of diagnosis were associated with a poorer clinical prognosis [25, 26, 27, 28, 29, 30]. Treatment generally consisted of surgical excision; adjuvant radiation was reserved for tumors that were not excised with widely negative margins.

The advent of immunohistochemistry and its application to soft tissue sarcomas in the 1980s and 1990s led to a series of investigations elucidating the immunoprofile of MFH. MFH was shown to frequently express vimen-

tin, actin, CD-68, and alpha-1-antitrypsin and alpha-1-antichymotrypsin. Other antigens reported to variably stain MFH included smooth muscle actin, desmin, keratin, epithelial membrane antigen, S-100 protein, and neurofilament [31, 32, 33, 34]. Most of these antigens are also commonly found in other tumors, including leiomyosarcoma, liposarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor, sarcomatoid carcinoma, and melanoma. Importantly, MFH was not found to express antigens specific to histiocytes, essentially proving that MFH was not a true histiocytic neoplasm [35, 36].

Well, if MFH is not a histiocytic neoplasm and its immunophenotype overlaps with other tumors, then what is its real nature? Some authors in the early 1990s strongly argued that MFH "constitutes a heterogeneous, non-cohesive collection of poorly differentiated tumors" and is "a term that has become a meaningless, diagnosis of convenience" [37]. This opinion was based on observations that poorly differentiated sarcomas may have a storiform-pleomorphic pattern and that according to some investigators, many of them can be reclassified as tumors other than MFH. Supporting this stance were two published studies that found that only approximately 16% of a combined group of 259 pleomorphic tumors, most of which were sarcomas, could be potentially classified as MFH [37, 38]. The results of these two studies, performed by the same senior author, have been repeatedly used as evidence to garner the notion that MFH does not exist as a distinct entity. However, both of these studies have some methodologic problems. For instance, in the larger study of 159 tumors, only one pathologist, who was also the sole author of the paper, reviewed the pathologic features of all of the cases. In the other series, new diagnostic categories were invented (pleomorphic myogenic sarcoma, possibly myogenic pleomorphic sarcoma, possibly myofibroblastic sarcoma), which included tumors that would otherwise be classified as MFH (i.e., MFHs that expressed myogeneic markers). Furthermore, both studies were largely based on morphology, which can be very subjective, and immunohistochemistry, the results of which were not quantified. Electron microscopy, which some consider the "gold standard" in identifying cell type, was performed in only 12% of cases.

The present

For better or worse, MFH was falling out of favor by the mid to late 1990s. In the new World Health Organization (WHO) classification of soft tissue tumors published in 2002, MFH was considered to represent a small group of undifferentiated pleomorphic sarcomas with no definable line of differentiation, and the term was used with caution and reluctance [39]. The myxoid variant was being preferentially classified as myxofibrosarcoma [40] and the angiomatoid variant, because of its indolent behavior, was removed from the family of MFH [41]. However, in the daily experience of many pathologists, there still existed a large group of pleomorphic sarcomas that had the morphologic features of MFH and that, after critical analysis, could not be reclassified as any other type of tumor. In fact, in 2000 and 2001, several series in combination reported the results of ultrastructural and immunohistochemical analyses of 318 cases of MFHs of soft tissue and bone [42, 43, 44]. Their results, as well as those of others, clearly indicate that MFH is composed of an admixture of neoplastic cells that have ultrastructural features indicative of fibroblastic and myofibroblastic differentiation. Specifically, the tumor cells are spindle and less frequently polyhedral in shape; the fibroblastic cells contain abundant dilated rough endoplasmic reticulum, intermediate filaments, and a prominent golgi apparatus and the myofibroblastic cells, in addition, have nuclear contractions, subplasmalemmal pinocytotic vescicles, and scattered thin filaments associated with dense bodies (Fig. 8) [42, 43, 44, 45]. The myofibroblastic phenotype explains why many of these tumors express actin, smooth muscle actin, and desmin, similar to normal and reactive myofibroblasts. Such tumors have the potential to be confused with other sarcomas, particularly leiomyosarcoma. In fact, in our experience, pleomorphic spindle cell sarcomas with the histologic and ultrastructural characteristics of MFH that immunohistochemically express muscle markers are frequently misdiagnosed as leiomyosarcoma. Some may argue that the limited sampling associated with electron microscopy is problematic in assessing these tumors. However, if MFH actually represented other tumor types in most cases, this would have become clearly evident in the large ultrastructural investigations of MFH. Therefore, some musculoskeletal pathologists are convinced that pleomorphic sarcomas with fibroblastic and myofibroblastic features form a distinct clinico-

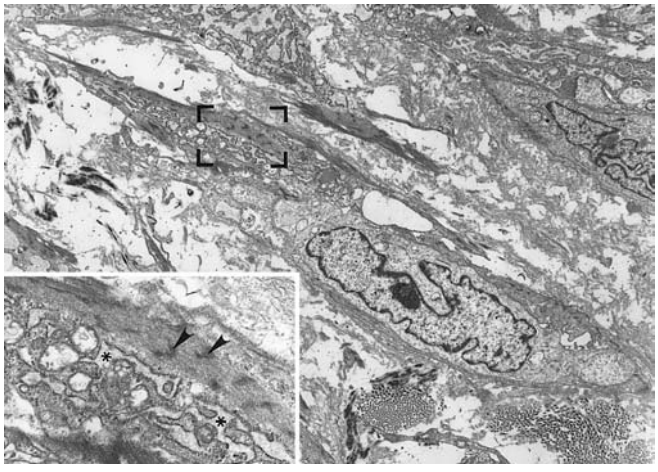

Fig. 8 Electron micrograph of a neoplastic cell in a MFH showing fibroblastic and myofibroblastic features. The abundant dilated rough endoplasmic reticulum (*) is characteristic of fibroblasts and the thin filaments with dense bodies (*arrowhead*) are typical of myofibroblastic differentiation

pathologic entity. That such a tumor exists and may even represent one of the most common groups of sarcoma should not be surprising. After all, fibroblasts are the most common mesenchymal cells in the body and benign and malignant neoplasms tend to recapitulate their normal tissue counterparts. Benign fibroblastic tumors form one of the largest groups of benign soft tissue tumors and it follows that malignant fibroblastic tumors may form one of the major groups of soft tissue sarcomas. This model is very similar to the relationships between adipocytes, lipomas, and liposarcomas and has ample biological precedence in many other organ systems. The observation that well-defined sarcomas of other cell lineages may contain areas identical to MFH does not negate the existence of pure pleomorphic fibroblastic and myofibroblastic sarcomas. On the contrary, the evidence supports the concept that these high-grade sarcomas contain a subpopulation of neoplastic cells whose genetic machinery drives them to express a fibroblastic/myofibroblastic phenotype. This puts the onus on pathologists to carefully examine every tumor so that its specific line(s) of differentiation, which determines nosologic classification, are identified.

The future

If it can be accepted that pleomorphic fibroblastic/myofibroblastic sarcomas do exist, what name most accurately reflects their nature? Certainly, the term MFH is well recognized and time-honored; however, it is scientifically inaccurate, as these tumors are clearly not histiocytic in nature. Diagnostic terminology must reflect the current understanding of disease states so that scientific advances can become incorporated into routine daily practice. As others have already proposed, the group of tumors encompassed by MFH should be incorporated into the category of fibrosarcoma [42, 44], as most, if not all fibroblastic tumors, are composed of cells with the features of fibroblasts and myofibroblasts. The subtypes of MFH could then be renamed as storiform-pleomorphic fibrosarcoma, myxofibrosarcoma, pleomorphic inflammatory fibrosarcoma, and giant cell rich fibrosarcoma (Table 1). To facilitate recognition of this change, editorials announcing the new terminology and the rationale behind it could be published in relevant journals. Although this new nomenclature would not be immediately translated into changes in the current treatment of these tumors, either for local or systemic control, it would provide an accurate classification scheme for future studies aimed at developing therapies targeted against sarcomas with specific phenotypes.

As new technologies are harnessed to help delineate cell lineage, they can be applied to the family of fibrosarcomas. The terminology of individual tumors could then be further refined, as necessary. However, such studies must be performed on well-characterized tumors to avoid the current problems associated with the new technique of gene expression profiling of sarcomas. To date, two published reports have described the gene expression profiles of a small number of MFHs and in both studies, the profiles were similar to those obtained from leiomyosarcoma. These results have been used to bolster the argument that MFH does not represent a separate diagnostic category [46, 47]. Unfortunately, neither of these studies provided any information regarding the immunohistochemical profile or ultrastructural features of the examined tumors. In one of these studies the authors found that the leiomyosarcomas segregated into two groups and only one of these groups had an expression profile similar to MFH. It is possible that the group of so-called leiomyosarcomas that were genetically similar to MFH represented inaccurately diagnosed MFHs with a myofibroblastic phenotype and the other group was composed of true leiomyosarcomas. In fact, one of the authors of this paper suggests that this problem likely occurred (J.X. O'Connell, personal communication). Lastly, another recently published analysis of gene profiling was not able to distinguish leiomyosarcoma from liposarcoma—does this mean that these two tumors are not distinct entities, as well? [48] Gene expression profiling is only in its early stages of testing and the significance of its results is still being defined. Additionally, it can not be overemphasized that the scientific validity of such studies is based on the accuracy of classification of the reference tumors; therefore, it is imperative that the tumors be properly classified by light microscopy, immunohistochemistry, electron microscopy, and, when appropriate, molecular analysis.

Studies utilizing new molecular techniques are substantiating the current classification schemes of sarcomas, which are based on observations made by morphologists decades ago. The optimal classification system should be exact and accurate, and, as the best evidence has been sifted through, it is evident that the pleomorphic fibroblastic sarcomas once championed by Stout need to find their valid position in the family of sarcomas.

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