Malignant Fibrous Histiocytoma
Between the Past and the Present
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The precise nature and diagnostic concept of malignant fibrous histiocytoma (MFH) has been debated for years. Currently, a histiocytic lineage of the tumor cells is no longer favored. The nomenclature and classification of MFH and its subtypes have also been changed. The MFH pattern, especially that of storiform-pleomorphic variant, is viewed as a morphologic pattern shared by a number of sarcomas as well as by other nonsarcomas. Therefore, a diagnosis of MFH based solely on morphology is no longer acceptable and identification of a line of differentiation should be sought. A diagnosis of MFH should be made only for pleomorphic sarcomas in which no specific line of differentiation is discerned. Precise categorization of MFH-like tumors may require thorough sampling of the tumor and judicious use of immunohistochemistry and/or electron microscopy. Familiarity with the current terminology and classification of MFH and its subtypes is of paramount significance in the modern practice of pathology.

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THE PRESENT VIEW OF MFH HISTOGENESIS

Although the term MFH gives the impression that the tumor cells are of fibroblastic and histiocytic origin, the precise origin has been disputed for decades. With the advent of diagnostic techniques such as cell cultures, immunohistochemistry, and electron microscopy, a large number of studies attempted to elucidate the histogenesis of MFH.4-6 The results of these studies are markedly conflicting, and often the disparity between the results is startling. Histiocytes, fibroblasts, or cells with features intermediate between fibroblasts and histiocytes, have all been proposed as the origin of the tumor cells.9,10 A primitive mesenchymal stem cell that then manifested with both fibroblastic and histiocytic differentiation to varying degrees has also been suggested.11 The bulk of evidence from all these studies suggests that MFH is a sarcoma of either fibroblastic or primitive mesenchymal origin, which manifests features of both fibroblastic and histiocytic differentiation. A true histiocytic origin is no longer acceptable.11 Nevertheless, until the definitive origin of the tumor cells is reached, the 2002 WHO classification has maintained the tumor under the “fibrohistiocytic” category.5

The “Common Pattern/Ultimate Pathway” Hypothesis

Malignant fibrous histiocytoma is now viewed as a common “morphologic pattern” shared by a number of pleomorphic neoplasms, irrespective of their differentiation. Thus, MFH brings together varying tumors that can be actually unrelated but share similar morphologic features. Malignant fibrous histiocytoma is also thought to represent a “final common pathway” for tumor growth. As tumors (either sarcomatous or nonsarcomatous) progress in their growth, they may lose their differentiation pattern to reach an ultimate undifferentiated pattern, which is common to all of these tumors. These hypotheses...
are supported by a number of published studies that re-evaluated tumors initially diagnosed as MFH. A specific line of differentiation (lipogenic, neurogenic, myogenic, or non-sarcomatous) was possible to ascertain in these cases. This may explain (1) the heterogeneity in immunophenotype, ultrastructure, and cytogenticities in many cases diagnosed as MFH; (2) the wide spectrum of clinical behavior (including treatment sensitivity, and time and pattern of metastasis), as well as the outcome of these cases; and (3) the frequent occurrence of MFH-like lesions in unusual locations. In a similar way, the morphologic characteristics of MFH subtypes are also found to be shared by a variety of other tumors, questioning their diagnostic entities and making it difficult to classify them under one category. Because of this view, the diagnosis of MFH and its subtypes became restricted to a small percentage of pleomorphic sarcomas in which all other possible lines of differentiation are excluded.1-3

NOMENCLATURE

The term MFH is perceived now as a misnomer because it points to a histiocytic origin of the tumor that is no longer tenable and it falsely includes unrelated tumors with a common morphology, as discussed earlier. Therefore, there are presently strong recommendations to abandon this term. Pleomorphic sarcoma is the alternate name advocated by the WHO to replace the current name as it gives a more accurate description of the tumor and does not imply the origin of the tumor cells.12 The term pleomorphic fibrosarcoma has been suggested13 but argued against because it may cause confusion with the classical fibrosarcomas, which are different entities consisting of a relatively uniform population of spindle cells almost always devoid of multinucleated or pleomorphic giant cells.14 Unfortunately, the term MFH is deeply ingrained in surgical pathology and very familiar to surgeons and clinicians. Therefore, it is recommended that when the new nomenclature is used, the term MFH should be placed alongside the new term. In this manner, the WHO maintained the term MFH in its 2002 classification of soft tissue tumors.5 Likewise, the same approach of tumor description appears in the American Joint Committee on Cancer 2002 staging system for soft tissue tumors.15 Maintenance of the term MFH in the tumor description, at least for the time being, may provide an opportunity for this conceptual evolution to be widely used until the old term loses its appeal.

REAPPRAISAL OF MFH SUBTYPES

Five subtypes of MFH are present. These are (1) storiform-pleomorphic, (2) myxoid, (3) inflammatory, (4) giant cell, and (5) angiomatoid subtypes. It has now become clear that these subtypes are heterogeneous entities that should not be classified under a single category.

Storiform-Pleomorphic MFH

Before the collapse of MFH and its subtypes as diagnostic entities, the storiform-pleomorphic subtype of MFH had comprised the overwhelming majority of MFH cases in the literature (60%-70% of cases).16 The storiform-pleomorphic MFH is typically composed of a mixture of spindled cells admixed with polygonal or rounded cells, arranged in a storiform pattern (Figure 1). A variable number of bizarre, multinucleated giant cells are also present. Marked cellularity and nuclear pleomorphism with abundant atypical mitoses are usually evident in this high-grade tumor (Figure 2). Storiform-pleomorphic MFH is usually found on the lower limbs of elderly patients (sixth and seventh decade). The retroperitoneum is also a common location. The aforementioned common pattern/ultimate pathway hypothesis is clearly represented in the storiform-pleomorphic MFH, in which the tumor morphology is shared by a number of undifferentiated tumors including sarcomas as well as nonsarcomatous tumors such as undifferentiated carcinomas (Figure 3), spindle cell melanomas, and spindle lymphomas. Therefore, the diagnosis of storiform-pleomorphic MFH is one of exclusion when no line of differentiation is identified. In such cases, an alternate name of undifferentiated high-grade pleomorphic sarcoma is being advocated by the WHO in its 2002 classification of soft tissue tumors. The tumor is still classified under the category of fibrohistiocytic tumors.3 After this conceptual shift, this subtype, which was once considered the most common soft tissue tumor in adults, now accounts for no more than 5% of adult soft tissue tumors.

Myxoid MFH

Myxoid MFH represented the next most common subtype of MFH (10%-20% of cases). Microscopically, the tumor shows prominent myxoid matrix. Myxoid MFH is now seen as a specific entity because not only does it have a distinctive myxoid appearance (Figure 4) but it has also been shown to have a better prognosis than other subtypes of MFH. Therefore, the 2002 WHO classification uses the term myxofibrosarcoma for this tumor.5 As myxofibrosarcoma displays myogenic differentiation (shows immunoactivity to smooth muscle or muscle-specific actin),17 myxofibrosarcoma has been removed from the fibrohistiocytic category and reallocated to the myofibroblastic one.5

Giant Cell MFH

Giant cell MFH was a rare variant (10%-15% of cases). The tumor is microscopically characterized by multinucleated giant cells. The giant cells closely resemble osteoclasts but their nuclei tend to be higher grade and are not usually found in association with osteoid. It is now appreciated that giant cell MFH does not represent a specific entity as it is usually possible to identify a line of differentiation in the majority of cases. Many cases initially diagnosed as giant cell MFH have been reclassified as giant cell–rich osteosarcoma, leiomyosarcoma with an osteoclastic giant cell reaction, or giant cell–rich anaplastic carcinoma.18 In cases in which no evidence of differentiation is found, diagnosis of giant cell MFH can be made, using its new terminology, which is undifferentiated pleomorphic sarcoma with giant cells. The tumor is classified under the category of fibrohistiocytic tumors in the 2002 WHO classification.5

Inflammatory MFH

Inflammatory MFH was the rarest variant (5% of cases). The tumor characteristically shows an intense inflammatory infiltrate that consists predominantly of neutrophils, lymphocytes, and foamy histiocytes (Figure 5). Similar to the other MFH variants, the entity of this variant has been questioned. Many cases initially diagnosed as inflammatory MFH were recognized to be dedifferentiated liposarcomas, in which the dedifferentiated component has a prominent stromal inflammatory infiltrate. Other tumors that closely mimic inflammatory MFH include anaplastic...
carcinomas with prominent inflammation and anaplastic large cell lymphomas. Therefore, the diagnosis of inflammatory MFH can be made only if no line of differentiation is identified. In the 2002 WHO classification, inflammatory MFH has been renamed as undifferentiated pleomorphic sarcoma with prominent inflammation and classified under the category of fibrohistiocytic tumors.

**Angiomatoid MFH**

Angiomatoid MFH is now no longer considered as an MFH subtype. This is because the tumor is morphologically and clinically distinct from MFH and its variants. The tumor occurs predominantly in children and young adults. Microscopically, the tumor is benign-looking with eosinophilic, oval, round, or spindled cells with slight pleomorphism, arranged in sheets and whorls. There are prominent slitlike vascular channels with an inflammatory infiltrate and focal areas of hemosiderin deposits and hemorrhage. Moreover, the tumor tends to run an indolent course with very infrequent metastasis. The benign nature of the tumor is reflected by its new name: angiomatoid fibrous histiocytoma. Although a myogenic differentiation of the tumor was evidenced by its desmin immunopositivity in about half of the cases, the precise line of differentiation is still unknown as concurrent epithelial differentiation is also frequently encountered (evidenced by its immunore-
activity to epithelial membrane antigen). Therefore, angiomatoid fibrous histiocytoma was removed from the category of fibrohistiocytic tumors in the 2002 WHO classification and reallocated to the category of tumors of uncertain differentiation.5

The Table lists the nomenclature and classification of MFH subtypes.

**DIAGNOSTIC APPROACH TO MFH-LIKE TUMORS**

Although it is emphasized that efforts should be expended to identify a line of differentiation in all MFH-like lesions, no published guidelines to define a diagnostic approach are available. However, careful and/or extensive sampling with the use of ancillary techniques, immunohistochemistry in particular, should be 2 important aspects of any diagnostic process.

**Careful and/or Extensive Sampling**

The diagnostic approach of any tumor resembling MFH can be initiated by careful sampling of the tumor in quest for areas that may help identify a line of differentiation. If the initial sections are not helpful in identifying a line of differentiation, additional sampling can help reveal more differentiated areas or at least some diagnostic features that were not present in the initial sections. In a published study,18 3 retroperitoneal lesions of dedifferentiated liposarcoma were initially misdiagnosed as MFH. This was because of lack of sufficient sampling as only 2, 3, and 1 paraffin blocks were performed on the 3 cases and none showed the well-differentiated liposarcoma component. The recurrent tumors were sampled extensively (37, 58, and 40 paraffin blocks). Areas of well-differentiated liposarcoma were seen on few slides, and in 1 case the well-differentiated liposarcoma component was seen on 1 slide only. Careful and extensive sampling was substantial in these cases to identify a line of differentiation and thus avoiding the erroneous diagnosis of MFH.

**Immunohistochemistry**

The use of immunohistochemistry is now essential in the diagnostic workup of any MFH-like tumor as it is now unacceptable to diagnose MFH based on morphology alone. Because the diagnosis of MFH is one of exclusion, an extensive immunohistochemistry panel is most likely required to exclude different lines of differentiation. There are no clear guidelines as to how extensive the panel of immunomarkers should be, but judicious use of immunomarkers should always be sought.12 The panel can start with immunomarkers of broad differentiation such as vimentin and cytokeratins for mesenchymal and epithelial differentiation, respectively. The panel can then be narrowed with more specific markers that can be added according to the clinical setting and histologic suspicion. Undifferentiated pleomorphic sarcoma typically demonstrates immunoreactivity to vimentin but fails to show reactivity to immunostains of other lines of differentiation (Figure 6). Contrary to what is traditionally known, histiocytic markers (CD68, α1-antitrypsin, α1-antichymotrypsin, and factor XIII) no longer play a useful role in the diagnosis of MFH as immunoreactivity to these markers is found to be nonspecific and, therefore, will not support a definitive diagnosis of MFH.22–24

**Electron Microscopy**

When the histomorphology and immunophenotype of the tumor are not distinctive enough for a specific diagnosis, electron microscopy can be an additional technique in searching for a line of differentiation in MFH-like tumors. Electron microscopy can provide answers when immunohistochemistry does not identify the tumor, especially when a tumor expresses small foci of apparently aberrant marker. For example, focal expression of cytokeratin or the presence of scattered smooth muscle actin–positive cells is not infrequent in undifferentiated pleomorphic sarcomas and should not be taken as evidence of carcinomatous or myogenic differentiation, respectively. In such cases, electron microscopy may confirm the differentiation line through finding the characteristic ultrastructural features.20

**Molecular Techniques**

Numerous studies have reported different genetic abnormalities in MFH, but conclusive cytogenetic data are not yet available, thus limiting the usefulness of molecular procedures in the diagnostic workup of MFH, at least for now.26

Until more ancillary studies are introduced, careful sampling and immunohistochemical studies are usually recommended toward obtaining the definitive diagnosis of MFH. Nevertheless, this diagnostic approach has some limitations. It is based on the assumption that significant amounts of tissue are available for extensive sampling. This may not be true, especially when core needle biopsies, which limit the amount of tissue available, are used. Moreover, the diagnostic workup can be exhaustive and costly if extensive sampling and a large panel of immunostains are required. Therefore, surgical pathologists have to pursue the most accurate and cost-effective interpretations within the constraints of time and cost. It is necessary that accurate and reproducible guidelines be drawn up to aid in logical and orderly search for lines of differentiation in MFH-like tumors.

**SIGNIFICANCE OF SEARCHING FOR DIFFERENTIATION IN MFH-LIKE TUMORS**

Searching for differentiation in MFH-like tumors can be clinically significant for therapeutic and prognostic reasons.
diagnosis of MFH as valid if the diagnosis is made on the basis of morphology alone, especially in the era before the introduction of immunohistochemistry. Moreover, the published clinical trials regarding the therapeutic modalities and prognosis of MFH should be updated with new therapeutic strategies restricted to the unclassifiable group of tumors—the pleomorphic sarcomas.

**CONCLUSIONS**

Malignant fibrous histiocytoma is a malignant soft tissue tumor composed of tumor cells without evidence of a specific tissue differentiation. It is now widely accepted that the so-called MFH is not a diagnostic entity as it represents a common, final pathway of many sarcomatous as well as nonsarcomatous tumors. Its features are shared by a variety of poorly differentiated malignant neoplasms. The term MFH is now reserved for the small group of truly undifferentiated pleomorphic sarcomas. In any MFH-like tumor, a line of differentiation should be searched for, leaving the unclassifiable or difficult-to-categorize lesions in the category of the formerly known MFH. If a line of differentiation is identified, the diagnosis should be made based on that specific differentiation. Careful sampling with the use of immunohistochemistry should prevent overdiagnosis of MFH. The tumor cells of MFH typically show a “vimentin only” immunophenotype, that is, diffuse immunoreactivity to vimentin with failure of other immunostains to discern any line of differentiation. The current classification and nomenclature of the entity formerly known MFH should be referred to while reporting the diagnosis.

**References**


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**Therapeutic Significance**

Because the MFH morphologic pattern is shared by many tumors of different lineages, identification of differentiation is of therapeutic significance because the tumors differ in the treatment modality. For example, poorly differentiated adenocarcinomas, spindled lymphomas, and melanomas can have MFH-like patterns but their treatment is different. If a diagnosis of MFH is erroneously given in such cases based on morphology only, inappropriate therapy would be instigated.

**Prognostic Significance**

Identification of subsets of pleomorphic sarcomas can be of a prognostic significance. For example, pleomorphic sarcomas with myogenic differentiation such as pleomorphic rhabdomyosarcoma usually show more aggressive behavior than pleomorphic sarcomas with nonmyogenic differentiation such as pleomorphic liposarcoma.

**CYTOLOGY**

Fine-needle aspiration of MFH lesions is usually of limited value in the differential diagnosis. The cytologic features of MFH on fine-needle aspirations are not specific and include clusters of atypical polygonal and spindle cells with bizarre, multinucleated giant cells (Figure 7). The neoplastic cells do not show cytomorphologic evidence of any specific tissue differentiation. Because an extensive immunohistochemical panel is usually required in the diagnostic workup of MFH-like tumors, it is unreasonable to expect a precise classification of these tumors based solely on fine-needle aspiration, especially if the cytology cases do not have enough cell block material to perform the immunocytochemistry. Therefore, it is better to avoid the diagnosis of MFH based on cytologic appearance alone. However, diligent search for cells or features that may help demonstrate specific differentiation (lipoblasts, rhabdomyoblasts, keratinization, and mucin production) should be attempted as this helps exclude the diagnosis of MFH.

Lastly, we have to point out that the shift in the diagnostic criteria of MFH has affected the literature. This change may affect the credibility of many reported MFH cases. Pathologists should exercise caution in accepting a


