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Review

Global protein-expression profiling for reclassification of malignant fibrous histiocytoma☆

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ABSTRACT

According to the newest World Health Organization (WHO) classification for soft tissue tumors in 2013, malignant fibrous histiocytoma (MFH) has been gone. Most sarcomas called MFH were reclassified to be high-grade pleomorphic forms of leiomyosarcoma, liposarcoma, rhabdomyosarcoma, and other sarcomas by recent molecular technologies. However, about 10% to 15% of sarcomas called MFH before, still cannot be given a precise classification, and these are now called undifferentiated pleomorphic sarcoma or are still called MFH. Further molecular approaches including proteomic approaches are imperative to classify these unclassified sarcomas for improving clinical outcomes of the patients with soft tissue sarcomas. This article is part of a Special Issue entitled: Medical Proteomics.

1. Introduction

Soft tissue sarcomas (STSs) are malignant mesenchymal tumors that develop in connective tissues, including fat, blood vessels, lymphatic tissue, muscles, and nerves. Traditionally, STSs have been categorized based on their histological similarity to normal connective tissue [1,2]. For the past 30 years, MFH has been the most common type of STS.

The only established treatment for MFH is surgery, with or without radiotherapy. According to previous reports [3–10], the five-year relapse-free survival of individuals with MFH can range from 39% to 64% [4,10], and the overall survival can range from 50% to 70% [7–10]. Although the use of chemotherapy should be considered in patients with MFH and a poor prognosis, the use of chemotherapy in treating MFH has been controversial.

According to recent molecular studies, the variety of pleomorphic STSs, which demonstrate various clinical behaviors, including various chemo-sensitivities and prognoses, may be included in the classification of MFH [11–13]. After the WHO classification for soft tissue tumors in 2002, MFH is no longer regarded as a distinct diagnostic category and according to the most recent WHO classification in 2013, a new category of 'undifferentiated/unclassified sarcoma (UPS)' has been created and MFH fall into this category. In the future, MFH has been disused and referred as UPS. However, the current classification system of WHO still permits the use of MFH as an alternate name, and many clinicians have used the term MFH [14,15]. To provide appropriate treatment, including chemotherapy, to individual patients with MFH, a reclassification of MFH is needed. An immunohistochemical approach [4,16], a comparative genomic hybridization (CGH) approach [17,18], and a cDNA microarray approach [19] have all been previously used to reclassify MFH (Table 1).

Emerging technology that examines the overall features of the expressed proteins (i.e., proteomics) has allowed for the detection of many proteins associated with tumor behaviors and possible clinical utilities, including early diagnosis [20], differential diagnosis [21], prognosis [22–24], and response to chemotherapy [25,26], in various malignant tumors. A proteomic approach, along with other molecular approaches, may also help in reclassifying MFH. In this review, we describe in chronological order the various approaches used to reclassify MFH and the possibility of using a proteomic approach in reclassifying MFH.

2. Confusing diagnostic criteria for MFH

In 1964, the diagnostic term "MFH" was first described by Stout et al. The authors described MFH as a distinct histological type of STS with a "storiform" or "matted" cell growth pattern on microscopic examination [1] (Fig. 1). In 1978, Weiss and Enzinger recommended that MFH

Abbreviations: STS, soft tissue tumor; MFH, malignant fibrous histiocytoma; UPS, undifferentiated pleomorphic sarcoma, WHO, World Health Organization; CGH, comparative genomic hybridization; LMS, leiomyosarcoma; DDLS, dedifferentiated liposarcoma; 2D-DIGE, two-dimensional difference gel electrophoresis

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Table 1
The classification of MFH in chronological order.

Date	1964 (Stout et al. [1]*)	1978 (Weiss and Enzinger [3]*)	2002 (Fletcher, Unni, and Mertens [2]*)	2013–at present [14, 15]*
Classification	MFH	Storiform–pleomorphics MFH Giant cell MFH Inflammatory MFH	Undifferentiated pleomorphic sarcoma	Variety of pleomorphic subtypes of sarcomas and the diagnostic term of MFH is gone away
		Myxoid MFH	Myxofibrosarcoma	
Treatment	Surgery and/or rediotherapy	Surgery and/or rediotherapy	Surgery and/or radiotherapy	Surgery and/or rediotherapy
Chemotehrapy	Controversial	Controversial	Controversial	Controversial
Morecular techniques for reclassification		1980 – Immunohistochemistry	1990 – 2000 CGH analysis The middle of 2000s cDNA microarray	The middle of 2000s – Proteomics analysis

*Reference number in this article.

be subcategorized into four variant histological subtypes: myxoid, storiform–premorphic, giant cell, and inflammatory [3] (Fig. 2). Unfortunately, not all investigators examined the prognostic value of each histological subtype of MFH, and thus, not all subtypes were equally represented or evaluated [27]. Therefore, the current understanding of the correlation between the histological subtype of MFH and prognosis as an independent variable is limited. These findings supported the idea that MFH and its histological subtypes are an insufficient risk-stratified classification.

In 2002, the WHO no longer considered MFH to be a formal diagnostic category; instead, it regarded it as a type of undifferentiated pleomorphic sarcoma or as an unspecified pleomorphic sarcoma [2]. The WHO reclassified myxoid MFH as myxofibrosarcoma, which belongs to the same classification as fibroblastic tumors (Fig. 2A); the remaining three subtypes (storiform–premorphic, giant, and inflammatory subtypes) were then considered to be undifferentiated pleomorphic sarcomas (Fig. 2B–D) [2]. Furthermore, the recent development of molecular techniques revealed that some forms of MFH may be reclassified with other histological STSs that show a wide spectrum of clinical behaviors, including various chemo-sensitivities and prognoses [4,12, 28–31] (Table 1). These confusing diagnostic criteria for MFH have led to a debate as to whether MFH is a valid clinicopathological entity or just a meaningless diagnosis of convenience for poorly differentiated STSs [12]. Thus, the current consensus is that MFH should not be considered to be a distinct diagnostic category and should be reclassified.

3. The importance of the reclassification of MFH for clinical outcomes and treatment strategies

A limited number of large retrospective clinical series [3,5–10, 32–42] concerning the clinicopathological characteristics of MFH have been published. The results from these series have not always agreed, and they are difficult to compare because of differences in the study objectives and designs. According to these reports, the five-year relapse-free survival can range from 39% to 64% [4,10], and the overall survival can range from 50% to 70% [7–10]. Given the controversies surrounding the diagnosis of MFH and given the likely inclusion of numerous types of sarcomas in the respective analyses and the lack of controls for tumor grade, such survival data sets are of limited value.

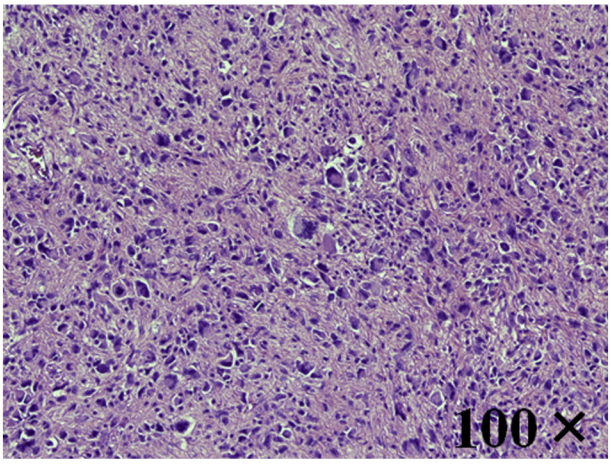

Fig. 1. The so-called MFH. MFH is associated with pleomorphic and bizarre tumor cells with a "storiform" or "matted" cell growth pattern upon microscopic examination.

Surgery with or without radiation therapy has been used to treat MFH, but the role of chemotherapy for MFH has been more controversial. The results from a meta-analysis of 14 available randomized trials of doxorubicin-based adjuvant chemotherapy showed a statistically significant improvement in the overall recurrence-free survival, a trend for improvement in the overall survival, and a significant improvement in the overall survival in patients with STSs that only affect the extremities, including MFH [43]. The interpretation of these studies has been controversial. Many investigators have argued that the selection criteria have varied too much in terms of poor confirmation of histology and grade. Most recently, a randomized study featured 104 patients with STSs; these patients were treated with high doses of doxorubicin and ifosfamide. The results of this study showed that the median disease-free survival increased from 16 to 48 months in the treatment group and that the overall survival increased from 46 to 75 months [44]. Chemotherapy supporters cite these studies as evidence of a benefit; detractors indicate that verification is required in other settings. Given the lack of conclusive data, the use of chemotherapy for treating MFH varies widely. The use of ifosfamide and doxorubicin should be considered in patients who are at greatest risk, and entry into a clinical trial should be encouraged. Efforts are underway to conduct more risk-stratified clinical trials to ensure that more distinct conclusions can be drawn with regard to the utility of given treatments [27]. Various types of STSs that demonstrate a wide spectrum of clinical behaviors, including various chemo-sensitivities and prognoses, may be included within the category of MFH. Therefore, the risk-stratified reclassification of MFH is particularly important for the treatment indication, including chemotherapy for patients with MFH.

4. A variety of approaches for the reclassification of MFH

An immunohistochemical approach [4,16], a CGH approach [17,18], and a cDNA microarray approach [19] have been applied to the reclassification of MFH in the past (Table 1).

Immunohistochemical studies convinced many clinicians and pathologists that MFH was a heterogeneous, non-cohesive collection of poorly differentiated STSs. The advent of immunohistochemistry in the 1980s led many pathologists to attempt to reclassify MFH [4]. Fletcher et al. reevaluated 100 tumors that were originally diagnosed as MFH. They found that leiomyosarcoma (LMS) and other myogenic pleomorphic sarcomas often shared pathological and morphological characteristics with MFH. They confirmed that most cases of supposed MFH can be classified by immunohistochemistry as other STSs, most commonly as LMS and other myogenic pleomorphic sarcomas. They also found that those other myogenic pleomorphic tumors, including LMS, had a worse prognosis, even those with the same American Joint Committee on Cancer stage and a shorter time to metastasis than non-

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