นิพนธ์ต้นฉบับ

Diagnostic criteria and concept of malignant fibrous histiocytoma: literature review and pathological study of 11 cases.

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Problem : *Today, there is no definite criteria and concept of malignant fibrous histiocytoma (MFH)*

Research objective : *To determine a reproducible criteria and concept of MFH*

Setting : *Department of Pathology, Faculty of Medicine, Chulalongkorn University*

Research design : *Descriptive study*

Material : *Specimens which were diagnosed as MFH between 1985 and 1994*

Methods : *Review the current concepts and suggested criteria of MFH from the literature and propose a reproducible, definite criteria for diagnosis. Those specimens were obtained and reevaluated by using the proposed criteria, which consisted of definite pleomorphic sarcomatoid morphology and no definite line of differentiation (adequate tissue sampling and extensive immunohistochemistry study). From extensive study, the results were as follows;*

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Results : - *Four cases were rediagnosed as liposarcoma, leiomyosarcoma, malignant mesenchymoma, and extra-abdominal fibromatosis.*
- *Two cases were unclassified due to inadequate tissue samples. Five cases fit the criteria for MFH, pleomorphic storiform pattern, which is believed to be a common pathway of soft tissue sarcoma.*

Conclusion : *This study should remind surgeons to take adequate samples of tissue, and the pathologists to carefully look for pleomorphic sarcomatoid patterns. Thus, we propose the new concept and diagnostic criteria for MFH, as a common pathway of differentiation in soft tissue sarcoma, not as a separate single entity as in the past.*

Key words : *Malignant fibrous histiocytoma, Pleomorphic sarcoma.*

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ธรรมธร อาศนะเสน, วรนุช ปัญญาวรวุฒิ, สุทธิดา อิงคตานุวัฒน์. เกณฑ์การวินิจฉัยของ malignant fibrous histiocytoma : โดยการศึกษาข้อมูลจากวารสารและการศึกษาทางพยาธิวิทยากายวิภาคในผู้ป่วย 11 ราย. จุฬาลงกรณ์เวชสาร 2540 ก.ค;41(7): 509-22

ปัญหา : *ปัจจุบันนี้ยังไม่มีข้อสรุปที่แน่ชัดและเกณฑ์การวินิจฉัยที่แน่นอนเกี่ยวกับ malignant fibrous histiocytoma (MFH)*

วัตถุประสงค์ : *เพื่อแสวงหาข้อสรุปความคิดรวบยอด และเกณฑ์การวินิจฉัยในทางปฏิบัติของ MFH*

สถานที่ศึกษา : *ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

แนวทางการศึกษา : *การวิจัยเชิงพรรณนา*

วัตถุดิบ : *ชิ้นเนื้อตัวอย่างที่ได้รับการวินิจฉัยเป็น MFH ตั้งแต่ปี 2528 ถึง 2537*

วิธีการ : *รวบรวม ความคิดรวมยอด และข้อเสนอแนะในเกณฑ์การวินิจฉัยต่างๆ ที่ได้รับการตีพิมพ์ในวารสารทางการแพทย์ล่าสุด เพื่อนำมาใช้ในการตั้งเกณฑ์การวินิจฉัย และหาข้อสรุปที่เป็นรูปธรรม*

ขั้นตอนการศึกษานี้จะนำเกณฑ์การวินิจฉัยนี้มาศึกษาย้อนหลังในวัตถุดิบดังกล่าวแล้ว เกณฑ์การวินิจฉัย คือ

1. *ลักษณะรูปร่างทาง H&E เป็น pleomorphic sarcomatoid*
2. *ไม่พบว่ามีแนวทางการพัฒนาไปเป็น sarcoma ชนิดอื่น โดยใช้ลักษณะทางจุลพยาธิวิทยา, การศึกษาโดยใช้ immonohisto-chemistry morphology, immunohistochemistry, และตัดเนื้อเพิ่ม*

ผลการศึกษา : *4 ใน 11 ราย ได้รับการวินิจฉัยใหม่ดังนี้ liposarcoma, leiomyosarcoma, malignant mesenchymoma, และ extraabdominal fibromatosis 2 ใน 11 ราย ไม่สามารถให้การวินิจฉัยได้ เนื่องจากชิ้นเนื้อที่ได้รับมีจำนวนน้อยเกินไป 5 ใน 11 ราย เมื่อพิจารณาตามเกณฑ์ แล้วได้รับการวินิจฉัยว่าเป็น MFH*

ข้อสรุป : *การศึกษานี้แสดงให้เห็นถึงความสำคัญในการสุ่มตัวอย่างจำนวนชิ้นเนื้อเพื่อการวินิจฉัยที่แน่นอนของเนื้องอกในกลุ่ม pleomorphic sarcoma และนำไปสู่ข้อสรุปใหม่ของ MFH ที่ว่าเป็นโรคที่เกิดในระยะท้ายสุดของ sarcoma ชนิดอื่นๆ โดยคิดว่ามี pathway เดียวกัน ไม่ใช่เป็นโรคที่จะสามารถจัดแยกออกเป็นโรคใดโรคหนึ่งอย่างที่เคยเข้าใจ*

Malignant fibrous histiocytoma is the most common soft tissue sarcoma of late adult life.[1] A definite diagnostic criteria and histogenesis of it had not been determined; hence, there was no true incidence and prevalence of this disease. MFH was first defined by Ozzello, et al and O'Briem and Stout in 1963 by the definition of a group of soft tissue tumours characterized by stori-form or cartwheel-like growth pattern.[2] Stout's original concept of histogenesis suspected that it derived from histiocytes which formed bimodel patterns of cells.[3] In 1972, Kempson and Kyriakos described 30 cases of fibroxanthoma.[4] That article defined the histologic appearances of the pleomorphic-storiform subtype of MFH. Wood GS in 1986 proposed supporting either fibroblastic or primitive mesenchymal cell differentiation.[5] Miettinem M, in 1990, failed to confirm monocyte-macrophage differentiation.[6] Leong, in 1993, revealed non-reactive staining of tumour cells by using the monoclonal antibodies to macrophage (HAM 56).[7] Recently, an alternative hypothesis has been that MFH, or at least the most common pleomorphic form, simply represents a common morphological manifestation of a variety of poorly differentiated sarcomas or more rarely, other neoplasms such as lymphoma and carcinoma.[8] This idea was raised originally by Snoves, et al,[9] Dehner,[10] and Brooks.[11] Further support for the concept of MFH as a common morphological manifestation of poorly differentiated tumours, particularly sarcomas, has been provided by a number of other studies.[8,12-14] However, some different concepts are still noted, such as pleuri-potential cells, which can differentiate toward tissue histiocytes or facultative fibroblasts[15] which originated from poorly differentiated fibroblast,[16] and of monocytic/histiocytic origin from cytokines study.[17] MFH was subclassified as pleomorphic-storiform, myxoid, giant-cell, and inflammatory patterns, according to morphology.[3] Angiomatoid MFH is subclassified as a separate entity in the intermediate MFH.[18]

In the many studies already mentioned, the diagnoses were based on their own criteria, and these were different from each other. Recent studies have tried to disclose the actual concept and diagnosis of MFH, as we did, for generalization and comparison with each other in the future. Here tried to propose applicable diagnostic criteria and guidelines for extensive investigations in the field of immunohistochemistry. Electron microscopic examination is not discussed in this report because of the limitation of the specimens.

In Thailand, we have found no literature that proposes a concept and diagnostic criteria of MFH, except for case reports. Therefore, this study is a pilot paper which attempts to clarify the existence of MFH in Thailand.

Materials and Methods

All informations about MFH were searched from "Medline" and "Local database" in CD-ROM of the library of Faculty of Medicine, Chulalongkorn University. These data relating to eleven cases of MFH, which were located in the

extremities and retroperitoneal areas, were obtained from the surgical files of the Department of Pathology, Faculty of Medicine, Chulalongkorn University. The data were collected between 1985 and 1994. All sections were reviewed according to the following criteria.[8]

Liposarcoma: The single existing criteria for the diagnosis of pleomorphic liposarcoma was the presence of multivacuolated lipoblasts. These were defined as large cells containing at least two (usually more) clearly defined, translucent intracytoplasmic vacuoles that distend the cell in such a way that often no other cytoplasm is evident.

Leiomyosarcoma: Leiomyosarcoma has been defined as expressing either desmin or smooth muscle actin and lack of cross striations. In addition, all cases show variably foci with a fascicular pattern of brightly eosinophilic spindle cells with blun tended vesicular nuclei, often with paranuclear vaculole.

Rhabdomyosarcoma: Rhabdomyosarcoma has been defined as expressing either actin or desmin and a compatible morphologic appearance of any type of rhabdomyosarcoma (embryonal, spindle, botryoid, and alveolar). Presentation of cross striations in the tumor cells is definite.

Malignant Peripheral Nerve Sheath Tumour : The diagnostic features are (a) demonstrable origin from a major nerve, (b) demonstration in pre-existent benign nerve sheath tumour or (c) development of an S-100 positive soft tissue sarcoma in a patient with neurofibromatosis.

Extraskeletal Osteosarcoma : The single criterion used in the absence of any other definable line of differentiation is the presence of bone or osteoid synthesized by cytologically malignant cells.

Malignant mesenchymoma : The single criterion used is the presence of two separate and distinct lines of malignant mesenchymal differentiation, by either morphology or immunohistochemistry. Patterns not accepted as specific were undifferentiated sarcoma, fibrosarcoma-like unclassified myxosarcoma, hemangiopericytoma-like, and pleomorphic MFH-like.

Non sarcomatous neoplasms : Diagnostic criteria varies substantially according to tumour type. Every diagnosis is supported by appropriate immunohistochemical data.

Malignant fibrous histiocytoma : There was a group of tumours in which, despite the use of clinical data and immunohistochemistry, a definable line of differentiation can not be identified. The sole remaining criterion is therefore a pleomorphic sarcomatoid morphology with clear evidence of malignancy. The tissue sampling must be adequate before diagnosis.

Electron microscopy is not used in this study due to non-availability of specimen.

The immunohistochemistry studies of all cases were newly stained, along the protocol of Fletcher CDM.[8] The antibodies that used in immunohischemistry were as follows: Vimentin (1:200), Desmin (1:200), Actin (1:200), S100 (1:10,000) Alpha-1-antichymotrypsin (1:6,000)

Lysozyme (1:4,000) Keratin (1:10,000), LCA (1:50), and CD68 (1:200). All antibodies were produced by DAKO company. The grading system on immunohistochemical staining based on these criteria was: 0-5% : 0, 6-25% : + 1, 26-60% : + 2, 61-75% : + 3, and 76-100% : + 4

Result

The final breakdown of revised diagnoses was shown in Table 1.

These diagnoses were made in strict accordance with the criteria as described above. The immunohistochemical data were summarized in Table 2.

Table 1. Final diagnoses rendered in 11 cases originally diagnosed as MFH.

Tumour type	No. of cases
Liposarcoma	1
Leiomyosarcoma	1
Extraabdominal fibromatosis	1
Malignant mesenchymoma	1
MFH, storiform-pheomorphic	5
Biopsy only*	2

* Small incisional biopsies were taken because of advanced stage of disease thus there were inadeqauate tissue samplings for diagnosing soft tissue sarcoma.

Table 2. The summary of reactive immunohistochemical result+

	VIM	DES	ACT	S100	A1ACT	LYS	KER	LCA	CD68
1. Liposarcoma	+3	-ve	-ve	-ve	+1	-ve	-	-	-
2. Leiomyosarcoma	+3	-ve	+3	-ve	+3	-ve	-ve	-ve	-
3. Extraabdominal fibromatosis	+1	-ve	-ve	-ve	+2	-ve	-	-	-
4. Malignant mesenchymoma	+4	-ve	+3	-	+4	+1	-	-	-
5. MFH : 1	+4	-ve	+1	-	+3	-ve	-ve	-	-
6. MFH : 2	+2	-ve	-ve	-ve	+2	-ve	-	-	-
7. MFH : 3	+4	-ve	-ve	-ve	+3	-ve	-	-	-
8. MFH : 4	+3	-ve	-ve	-ve	+2	-ve	-ve	-	-
9. MFH : 5	+1	-ve	-ve	-	+4	-ve	-ve	-	-
Biopsy only									
10. 1	+4	-ve	-ve	-	+3	-ve	-	-	-ve
11. 2	+4	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-

\+ Selection for immunohistochemistry was based on morphologic examination (H&E staining) VIM, vimentin; DES, desmin; ACT, smooth muscle actin; A1ACT, alpha-1 antichymotrypsin, LYS, lysozyme; KER, pankeratin; and LCA, leukocyte common antigen.

Liposarcoma : One case was diagnosed as liposarcoma, pleomorphic type. (Fig 1) He was a 24-year-old male patient who had a mass in his left upper arm, measuring 2.0x0.5 cm.

Leiomyosarcoma : One case was diagnosed as leiomyosarcoma, pleomorphic type (Fig2). He was a 51-year-old male patient with intraabdominal mass, measuring 21x15x9 cm. This mass was attached to the stomach and colon.

Extra-abdodminal fibromatosis : One case was diagnosed as extra - abdominal fibromatosis (Fig 3). He was a 50-year-old male patient with mass in his left thigh, measuring 8.0 x 1.5 x 0.3 cm.

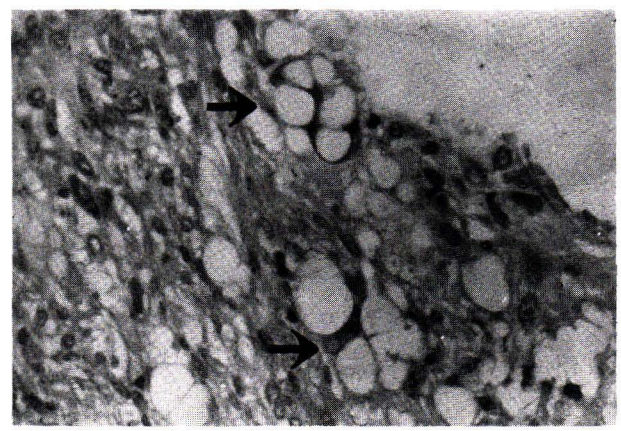

Figure 1. Illustrates lipoblasts (arrows) which contain multiple vacuoles in cytoplasm that is the characteristic picture of liposarcoma. (H & E stained, X 400)

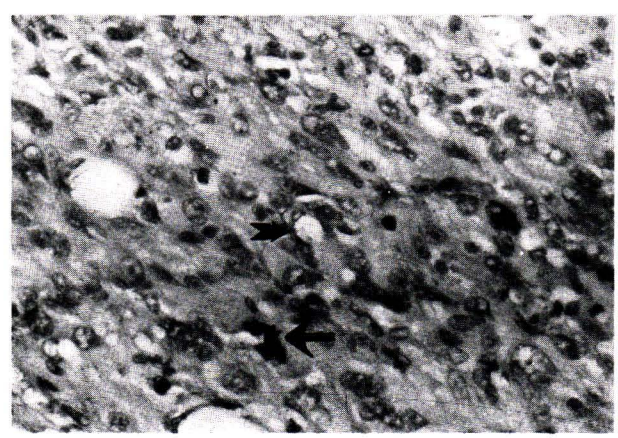

Figure 2. Illustrates typical pattern of leiomyosarcoma which has cigar-shaped nuclei with paranuclear glycogen vacuoles (thin arrow) and markedly atypical mitoses (thick arrow) (H & E stained X 400)

Figure 3. Illustrates bland-looking spindle cells with heavily collagenized stroma which is the finding in extraabdominal fibromatoses. (H & E stained, X 100)

Malignant mesenchymoma : One case was diagnosed as malignant mesenchymoma (Fig. 4 and 5), which was composed of leiomyosarcoma with prominent osteoclast-like giant cell[19] and liposarcoma. He was a 66-year-old male who had a mass in his left thigh, measuring 17.2 x 12.5 x 3.5 cm.

Malignant fibrous histiocytoma : Five cases fit the diagnosis criteria of MFH (Fig 6) which was pleomorphic-storiform pattern. The ratio of affected women to men was 3:2. The ages ranged from 24 to 70 years. The mean age was 54 years. The only common symptom of all was a mass. The locations were variable and consisted of the small bowel

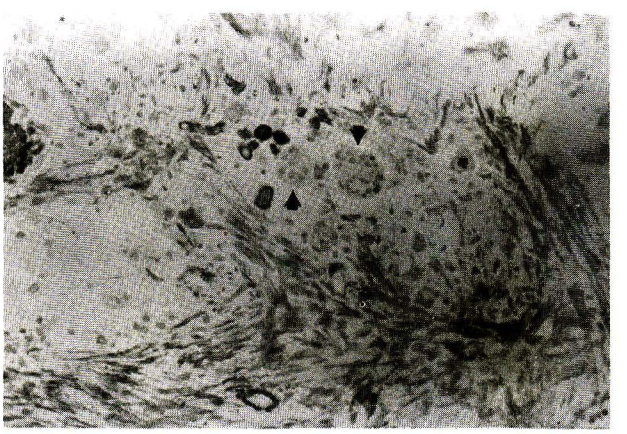

Figure 4. Illustrates spindle cells that stain for smooth muscle actin. Multinucleated giant cells (arrows), which are reactive, are noted. These findings are characteristics of leiomyosarcoma with prominent osteoclast-like giant cells (Smooth Muscle Actin, X 200)

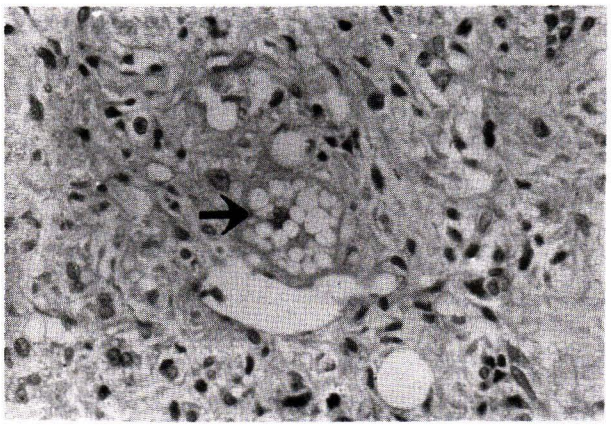

Figure 5. Illustrates focal areas of lipoblasts (arrow) in the same tumour as figure 4. These pictures are classified as malignant mesenchymoma that contains leiomyosarcomatous and liposarcomatous components. (H & E stained, X 400)

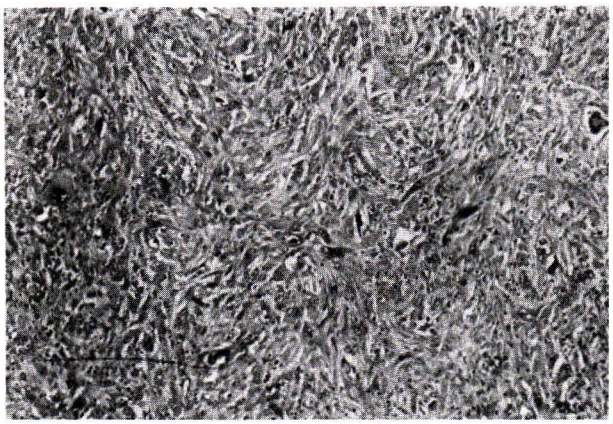

Figure 6. Illustrates storiform (whorl) pattern of pleomorphic cells which devoid of definable line of differentiation and fit to be MFH. (H & E stained, X 100)

(extraluminal), buttock, medial aspect of left upper leg, right lumbar area, and abdominal wall. The size of the tumours ranged from 10 to 20 cm in each greatest dimension. A history of recurrence was obtained in four patients whose primary lesions were diagnosed as fibrosarcoma, neurilemmoma, MFH and there was no indication of previous diagnosis in one case.

Biopsy only : Of these five cases, two were too small incisional biopsy specimens because of the advanced stage of disease. Despite considerable effort, these could not be categorized in the manner of the preceeding cases; thus we did not consider them as possible examples of MFH because of the significant problem of inadequate tissue sample. The limitation of specimen was not considered because they did not represent all morphologies or features such as lipoblast or better differentiated areas which were used to provide definite diagnosis.

Discussion

The results of reanalyzing these eleven tumours which were originally diagnosed as MFH can be interpreted in different ways and, to some extent, is a matter of personal opinion. Although accepting the importance and validity of such opinions, it is our aim to assess these results in a logical, defensible, and reproducible manner. We believe that the demonstration of a definable line of differentiation in 45.46% of these cases can be used to rule out the diagnosis of MFH. In conclusion, we depended on the strict criteria that we had established.

About the immunohistochemistry, it is necessarily utilized to exclude other soft tissue sarcomas (or even carcinoma and lymphoma) that can be detectd by this technique as in our study and review litrature. However, some tumours such as osteosarcoma, liposarcoma, and fibrosarcoma have no specific marker for detection by this method. The argument that actin expression in one case simply reflects the presentation of myofibroblasts in MFH is raised. In our case, it has focal areas that display typical leiomyosarcomatous appearance. Whether this lesion is smooth muscle or myofibroblasts seems to be less important than recognizing it as a definable phenotypic subset of pleomorphic sarcomas which are distinct from so-called MFH.

Others have confirmed that differentiated features may be present only in a minority of cells in pleomorphic sarcomas,[8,19] hence this raised the potential problem of sampling error and this threw into doubt the existence of MFH. Therefore, two cases were excluded in this study.

At present, however, subclassification of adult pleomorphic sarcoma is of little value or no significant help for treatment or prognosis.[2,8] Using histiocytic markers for diagnosis of MFH is still controversial. Some experiments exhibited reactive tumour cells by CD68 or KP.1,[14,16,18,20,21] but some experiments exhibited non-reactive tumour cells by CD68[2,3] or HMA56.[7] There were evidences that KP1 (CD68) is not specific marker for histiocyte/myeloid cells, so this marker was not included in our criteria for diagnosis.

In our study, the numbers of specimens were too few to compare with the epidemiologic studies of Weiss SW and Enzinger FM which were based on 200 cases.[1] Our data is also rather different from those series in terns of peak age and location. However, there were also some reported cases of other rare primary locations except for extremities which are the most common sites. The rare sites were as follows: suboccipital region,[22] left infraorbital region,[22] ulcer at left supra-clavicular region[22], pleura[23], spermatic cord[24], breast[25],brachial plexus[26] (radiation induced), kidney[27], floor of mouth[28], right ventricle of heart[29], left atrium[30], mandible[31], liver[32], prostate[33], transverse colon[34] (radiation -induced), vulva[35], omentum of infant[36], larynx[37], lung[38], and pericardium.[39] A reported case of synchronous occurrence of MFH and bronchogenic carcinoma was also present.[40]

As for cytologic diagnosis by FNA, an

extensive literature review indicates there has been no actual study about this topic except for a letter to the editors of Villanueva RR. in Acta Cytologica 1995 that exhibited some picture in cytology, includingthe useful immunohistochemistry.

From our study, we isolated some foci which displayed more differentiation, especially in recurrent cases like those reported by Fletcher[8] and Cesta MJ[14]. Two recurrent cases which were previously diagnosed as MFH also exhibit more mature histologic appearance and immunohistochemistry profiles (extraosseous osteosarcoma and leiomyosarcoma). As foremen-tioned evidences in this paragraph, they bring to why the Fletcher's criteria[8] are the most intersting and why the MFH is supposed to be the common pathway of the soft tissue sarcoma.

Conclusions

The proposed diagnostic criteria is diagnosis by ruling out the definite line of differentiation under condition of adequate tissue sampling and extensive appropriate immuno-histology. The diagnostic criteria are based on the concept that MFH is a common pathway in soft tissue differentiation.

Such findings suggest MFH. Finally, we beleive that MFH is a common pathway in soft tissue diferentiation and is located between hypothetical primitive mesenchymal stem cells and more differentiated sarcoma(diagram 1). However, this new concept about MFH is still questionable by some authors in reproducibility.

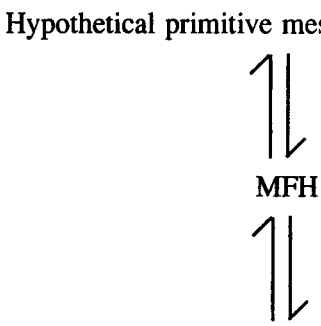

Diagram 1. Postulated concept of MFH.

At least, it merely a pilot study to declare the criteria that will be proof in the future so far so good.

However, there is still a group of pleo-morphic sarcomas in which the definite line of differentiation is not present, matching with MFH, but we expect that further examination, such as via electron microscopy, cytogenetic study, or follow-up in recurrent mass, will clearly specify differentiation.

At that time, the overdiagnosis will be decreased and MFH may lose its position of preeminence in sarcoma pathology.

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