

Original Article

Myofibroblastic sarcomas: a clinicopathologic analysis of 15 cases and review of literature

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Abstract: To analyze the clinicopathological, immunohistochemical, and histochemical characteristics of myofibroblastic sarcoma arising in different locations to improve the knowledge of this disease. Retrospective study of 15 myofibroblastic sarcoma cases and literature review. The patients included seven males and eight females (age, 6-73 years; mean, 46.6 years). A painless mass was the main clinical symptom. Histologically, the tumor cells were mostly solitary with non-clear cell boundaries; fusiform, oval cells with eosinophilic cytoplasm arranged in a fasciculate, woven pattern were observed. Fat spindle cells, spindle cells, or fine wavy nuclei with pale staining and small eosinophilic nucleoli were noted. Immunohistochemically, most cells were positive for vimentin, calponin, fibronectin, and smooth muscle actin; few cells showed positive desmin staining; and all were negative for h-caldesmon. Van Gieson and Masson stains showed mixed yellow/red and red/blue staining, respectively. During the clinical follow-up of 14 patients, five and one experienced local recurrence and distant metastasis, respectively, one died, while the other seven were alive with no evidence of disease. Myofibroblastic sarcoma is a rare mesenchymal malignant tumor prone to relapse. It resembles fibrosarcoma, malignant fibrous histiocytoma, and leiomyosarcoma in morphology and is easy to misdiagnose. Correct diagnosis requires morphological, histochemical, and immunohistochemical analyses.

Keywords: Myofibroblastic sarcoma, immunohistochemistry, histochemistry, diagnosis

Introduction

As its name implies, myofibroblastic sarcoma (MS) is a malignant tumor mainly composed of myofibroblasts. Whether or not myofibroblasts as a tumor component constitute a real tumor is controversial, and the diagnostic criteria of MS have been the focus of many research efforts [1, 2]. Some scholars do not recognize the existence of myofibroblastic tumors, even though smooth muscle or fibroblastic tumors accompanied by myogenic differentiation have been well described. Finally, in 2002, the World Health Organization (WHO) classification of bone and soft tissue tumors included a new disease entity-low-grade MS-and thus affirmed the objective existence of such tumors [3]. However, the moderate-to-high grade forms of the tumor have not been formally defined in the WHO classification, and this has resulted in the

pathological diagnosis being difficult and in the misdiagnosis rate being high [4].

In this study, we analyzed 15 cases with complete pathological examinations and reviewed the literature to further analyze the clinicopathological features of MS as a means to improve the understanding of this disease.

Materials and methods

Patients and tissue samples

Fifteen cases of MS were collected from our department from 2010 April to 2014 May. These cases included 13 and two cases of external examination and consultation, respectively; another two cases each of leiomyosarcoma and fibrosarcoma were selected as controls. All cases were reconfirmed by two senior pathological experts. The clinical information

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Table 1. Primary antibodies used in this study

Antigen	Source	Clone	Dilution
Vim	MaiXin	V9	1:100
SMA	MaiXin	IA4	1:100
MSA	MaiXin	HHF35	1:100
calponin	MaiXin	CALP	1:100
LN	MaiXin	LAM-89	1:50
h-caldesmon	MaiXin	h-CALD	1:100
FN	MaiXin	Poly	1:300
Des	MaiXin	D33	1:100
S-100 protein	MaiXin	4C4.9	1:100
ALK	MaiXin	Poly	1:100
CK	MaiXin	AE1/AE3	1:100
CD34	MaiXin	Qbend/10	1:400
Ki-67	MaiXin	MIB-1	1:100

and follow-up data were directly obtained from the hospital records and from the patients.

Histochemistry and immunohistochemistry

The tissues were fixed in 10% buffered formalin and embedded in paraffin. Histological sections (4 μ m) were created and stained with hematoxylin and eosin (HE), Masson's trichrome, and van Gieson (VG) staining at the same time; leiomyosarcoma and fibrosarcoma tissues were used as a comparison. By using the streptavidin-peroxidase method (3,3'-diaminobenzidine coloration), the paraffin-embedded sections of all 19 cases (including the controls) were immunohistochemically analyzed. The antibodies used and their concentrations are listed in **Table 1**. The primary antibodies (all from the same manufacturer, Fuzhou Maixin Biotechnology Co., Ltd. Fujian, China) included: vimentin (Vim), desmin (Des), muscle-specific actin (MSA), h-caldesmon, calponin, cluster of differentiation 34 (CD34), anaplastic lymphoma kinase (ALK), and laminin (LN), smooth muscle actin (SMA), fibronectin (FN), and epithelial membrane antigen (EMA), S-100, and Ki-67. Positive and negative immunohistochemistry controls were set up. The leiomyosarcoma tissues served as positive controls for SMA, calponin, h-caldesmon, and LN, while the fibrosarcoma tissues were used as positive controls for Vim and FN, with PBS instead of the primary antibodies as the negative control. The specimen was regarded as positive when the staining area of above medium intensity in the tumor tissue was more than 25%, whereas no coloration or focal, weak positive staining was de-

finied as negative staining. According to the French National Cancer Institute System for grading standards for soft tissue tumors [5], that is, mild nuclear atypia of tumor cell with no tumor necrosis and the mitotic figures (0-5 per 10 high-power fields) is low grade. moderate nuclear atypia of tumor cell with tumor central visible necrosis and the mitotic figures (6-10 per 10 high-power fields) is moderate grade. Obvious pleomorphism and exotic nuclei of tumor cell with 15% more tumor necrosis is high grade.

Statistical analysis

SPSS v. 17.0 statistical software (SPSS Inc., Chicago, IL) was used for the statistical analyses. The partial clinicopathological parameters between low-grade and moderate-to-high grade MS were evaluated by the Chi-square and Fisher's exact tests. A two-sided significance level of 0.05 was considered statistically significant.

Results

Clinicopathologic features of MS

The main clinicopathological features of the 15 cases of MS are shown in **Table 2**. The patients reported in the study included seven male and eight female patients, aged 6-73 years (mean age, 46.6 years). The lesions involved the soft tissue of the head and neck region and jawbones (n=6), trunk (n=3), thigh (n=3), tibia (n=1), lung (n=1), and the top of the head (n=1). A painless enlarging mass was the main clinical symptom. Of all 15 patients, 14 were treated by surgical operation, with eight (cases 1, 3, 4, 5, 8, 10, 11, 15) receiving postoperative radiotherapy. Except one case lost to follow-up, clinical follow-up information of 14 patients was available over a mean duration of 26 months (range, 6-44 months). During the follow-up period, five patients experienced local recurrence, 13 to 33 months after the initial operation; one developed distant metastasis 16 months after the initial operation; and seven (45%) were alive without evidence of disease at the latest follow-up. In one case (case 9), only centesis was performed. In this case, after the definite diagnosis of the mass was made, another larger mass was found in the abdominal cavity, and without further treatment, the patient died 6 months later.

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Table 2. Clinicopathological data of 15 cases of MS

Case	Gender	Age	Location	size# (cm)	Depth	Tumor grade	Treatment	Follow-up (months)	Follow-up Results
1	M	6	Left hip	5.0	Intramusculary	Low	Expanded excision	11	NR
2	M	14	Top of the head	3.0	Subcutaneous	Low	Simple mass excision	-	L
3	M	17	Right maxillary sinus	8.0*	Inside Maxillary sinus	middle	Right maxillary resection	19	R
4	M	31	Right mandible	2.5	Inside the mandible	Low	Right mandibular resection	18	NR
5	F	32	Left waist and back	5.5	Subcutaneous and muscular	Middle	Expanded excision	40	NR
6	M	38	Right lower lung	2.0	Lung parenchyma	Low	Right lower lobectomy	34	NR
7	F	43	Right tibia	4.0*	Inside the tibia	Low	lesion was scraped and bone graft	33	R
8	F	52	Right face	2.0	Dermis and subcutaneous	Low	Simple mass excision	44	NR
9	F	55	Right armpit	5.5	Subcutaneous and muscular	Middle	Needle biopsy	6	D
10	F	65	Left thigh	12.0	Intramusculary	High	Expanded excision	16	M
11	F	65	Right thigh	10.0	Intramusculary	Middle	Expanded excision	13	R
12	M	66	Right cheek	1.5	Submucosal	Low	Simple mass excision	36	NR
13	F	70	Left thigh	6.0	Intramusculary	Middle	Expanded excision	31	R
14	F	72	Right preauricula	2.5	Dermis and subcutaneous	Low	Tumor removal	23	NR
15	M	73	The throat	2.0	Mucosal and submucosal	Low	Partial laryngectomy	30	NR

*broken tissue; size#: tumor major diameter. Abbreviations: M: male; F: female L: lost of follow up; NR: no recurrence, (months); D: death; R: recurrence; M: metastasis.

Morphologic features

Most tumors were single nodular masses, while two cases showed broken tissue. The size of the tumors ranged from 1.5 to 12.0 cm in diameter (mean, 4.8 cm). The boundaries of most masses were not clear, and one case showed incomplete encapsulation. Six, five, three, and one cases were located in the muscle, subcutaneous or submucosal tissue, bone tissue, and lung parenchyma, respectively. The tumor tissues showed mostly infiltrative growth and invaded into the surrounding adipose and skeletal muscle tissue (**Figure 1A**). The tumors occurring in the bone showed invasion of the bone surface and bone tissues of varying degrees.

Histologically, the tumors were composed of spindle cells with fascicular, loosely woven, or vaguely storiform arrangement. The spindle cells were relatively uniform, closely arranged, and often accompanied by varying degrees of local cell density and arrangement structure changes (**Figure 1B**). The tumor cells contained eosinophilic or weakly eosinophilic cytoplasm with indistinct cell boundaries, and some cells were characterized by the cytoplasmic tail being located to one side of the nucleus (**Figure 1C**). Moreover, their nuclei were oval or tapering, some were slender, spindle-shaped, or wavy with moderate hyperchromatic structures, and a few fat spindle or nearly round vesicular nuclei with small red nucleoli were observed. In addition, we could observe different degrees of nuclear atypia, ranging from mild atypia and

pleomorphism to moderate atypia and obvious pleomorphism, with varied number of mitotic figures (1-12 per 10 high-power fields) (**Figure 1D**). Pathological karyokinesis and necrosis were observed in three cases, and scattered multinucleated giant cells and exotic nuclei were seen in two cases (**Figure 1E**). The tumor stroma was characterized by collagenous matrix with different degrees of hyaline degeneration, local mucoid degeneration, a thin wall of slit-shaped or branched small vessels, and varying degrees of lymphocyte and plasma cell infiltration in some cases (**Figure 1F**).

Immunohistochemistry

The tumor cells showed extensive, moderate-to-strong positive expressions of Vim, SMA, MSA, and FN in all cases (**Figure 2A, 2B**), of calponin in most cases, and of Des in a few cases. Focal positive staining for CD34 and S-100 were observed, whereas the tumor cells were negative for h-caldesmon, cytokeratin (CK), ALK, and LN. The Ki-67 index differed according to the grade, ranging approximately 8-45%. The two cases of leiomyosarcoma showed positive expressions of Vim, SMA, calponin, h-caldesmon, and LN, while the two cases of fibrosarcoma were positive for Vim and FN, but negative for the myogenic markers.

Histochemistry

Histochemically, through Masson's trichrome and VG staining, we found that the tumor tis-

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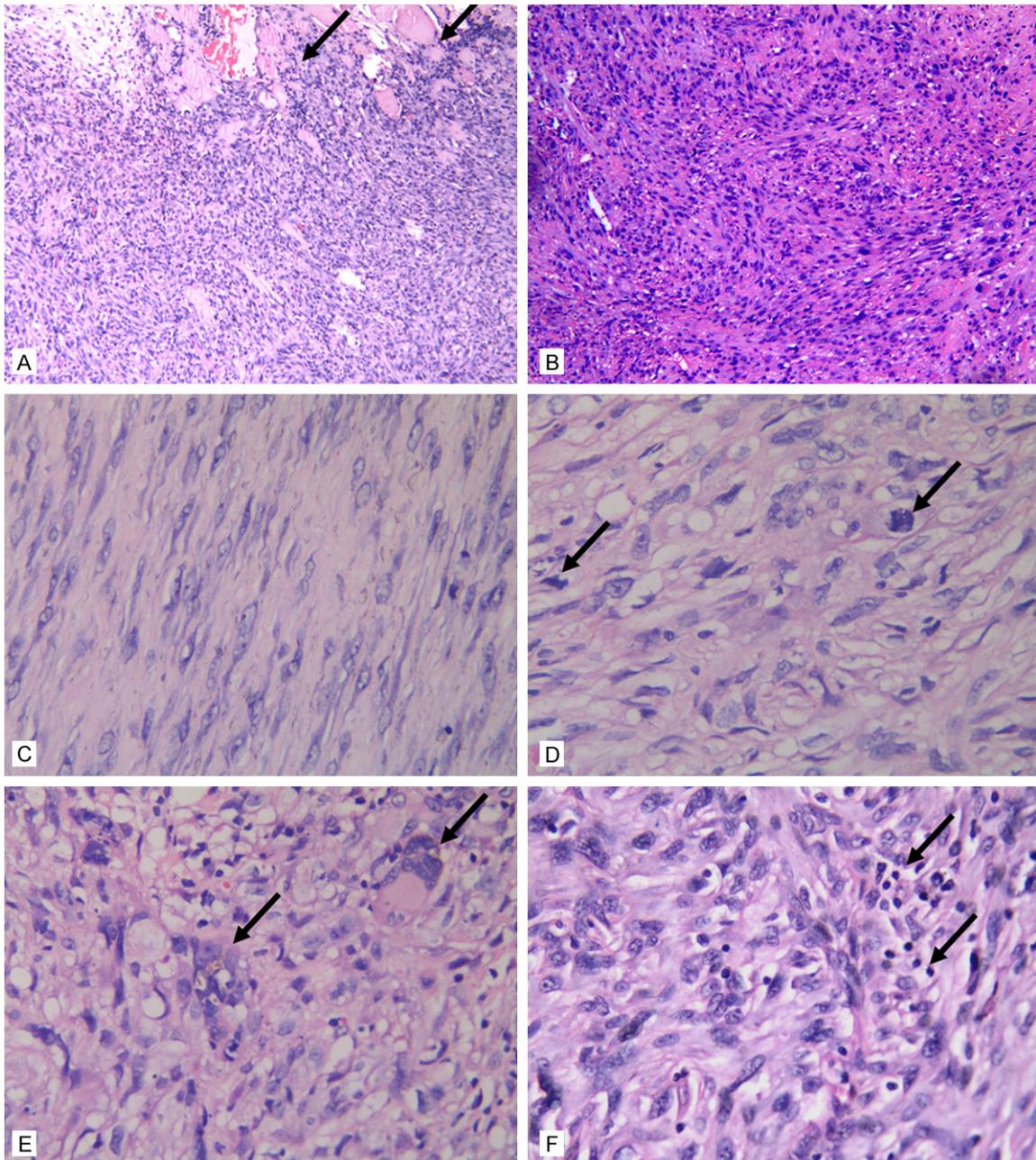


Figure 1. The representative micrographs showing of myofibroblastic sarcomas (HE stain, original magnification, $\times 100$ for A and B; $\times 400$ for C-F). A. The spindle tumor cells invaded into the surrounding skeletal muscle tissue (indicated by arrow above). B. The tumor was composed of spindle cells with fascicular, loosely woven or vaguely storiform arrangement. C. Some cells were characterized by cytoplasmic tail to the one side of the nucleus. D. The tumor cells showed moderate atypia and karyokinesis (indicated by arrow above). E. Scattered multinucleated giant cells and exotic nuclei (indicated by arrow above), (case No. 9, 10). F. A few of lymphocytes infiltration in tumor tissue (indicated by arrow above).

sues stained red/yellow and blue/red, respectively (**Figure 3A, 3B**). For each stain, the proportions of the two colors were largely similar, with each color representing more than 30% of the tissue specimen. In contrast, the two cases

of leiomyosarcoma showed only yellow and red staining upon the VG stain and Masson's trichrome staining, respectively, while the two cases of fibrosarcoma showed only red and blue staining, respectively (**Figure 3C, 3D**).

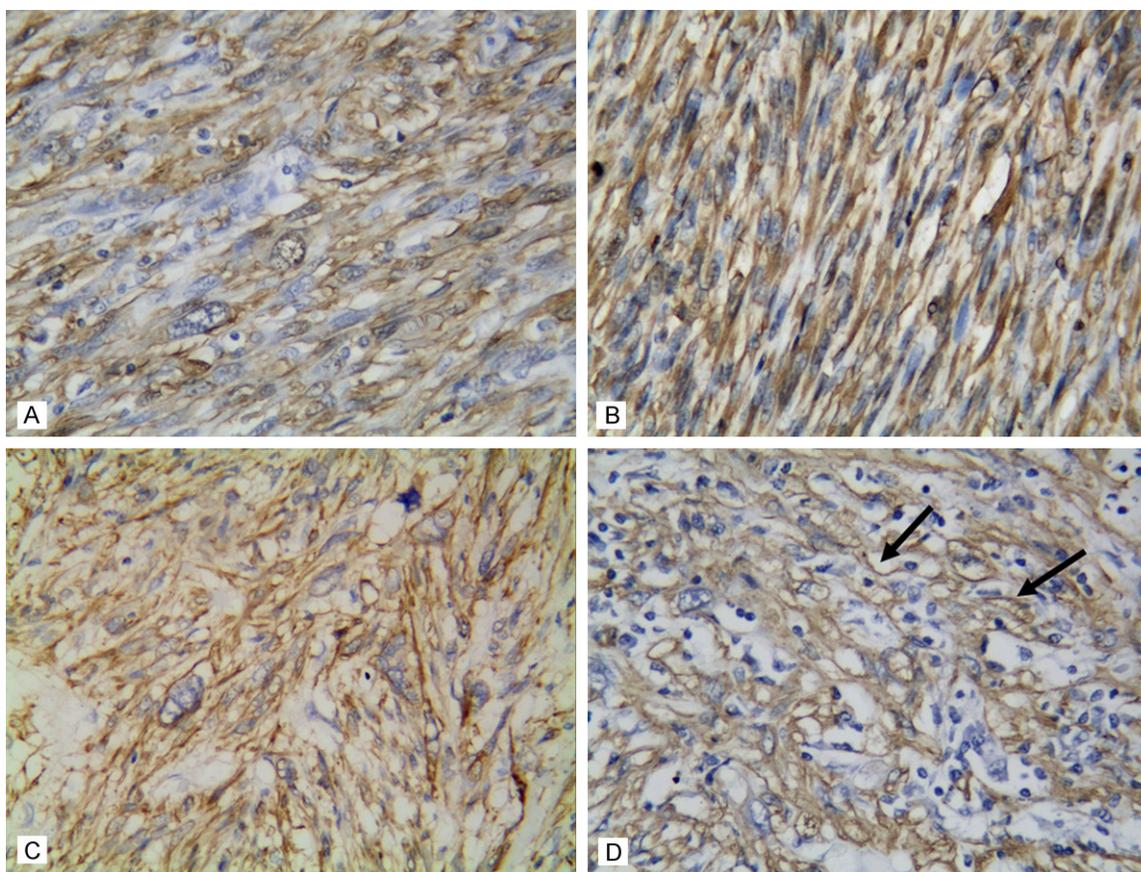


Figure 2. Immunohistochemical staining of MS (SP, original magnification, $\times 400$ for A, C and D; $\times 100$ for B). A. Diffuse cytoplasmic and membrane positive immunostaining for FN. B. Extensive and strong cytoplasmic positive staining for calponin. C. Extensive and strong cytoplasmic and membrane positive staining for SMA. D. Tumor cells showed the expression pattern of linear enhancement located in the cytoplasm around the membrane for SMA (indicated by arrow above).

Comparison of partial clinicopathological data between low-grade and moderate-to-high grade MS

We compared the partial clinicopathological data between low-grade and moderate-to-high grade MS and found significant differences in tumor size, mitotic index, and proliferation index between the groups. There were no significant differences between the groups in terms of age, lymphocyte and plasma cell infiltration, recurrence, and metastasis (**Table 3**).

Discussion

Myofibroblasts were originally described and defined by Gabbiani et al. [6] by means of electron microscopy. These cells show certain characteristics of both fibroblasts and smooth muscle cells, and are widely found in damaged human tissues, inflammation and tissue repair, and in mesenchymal tumors. In 1978, Vasudev

et al. [7] first reported the pathological features of MS. Since then, only a few related case reports and series have been reported in the literature. In 1998, Mentzel et al. [8] using immunohistochemical and ultrastructural observations, confirmed this tumor in a series of patients and named it “low-grade myofibroblastic sarcoma”. In 2001, Montgomery et al. [9] reported on a group of similar cases, and further clarified the morphological diagnosis standard of this disease. In the 2002 WHO classification of soft tissue and bone tumor pathology and genetics, low-grade MS was for the first time classified as a distinct entity. In the subsequent versions, it is still referred to as low-grade MS and classified as part of the fibroblastic/myofibroblastic tumor category [10]. However, although only low-grade MS is included in the WHO classification, moderate-to-high grade tumors have also been reported in the literatures [11, 12], especially in recent years [13-17].

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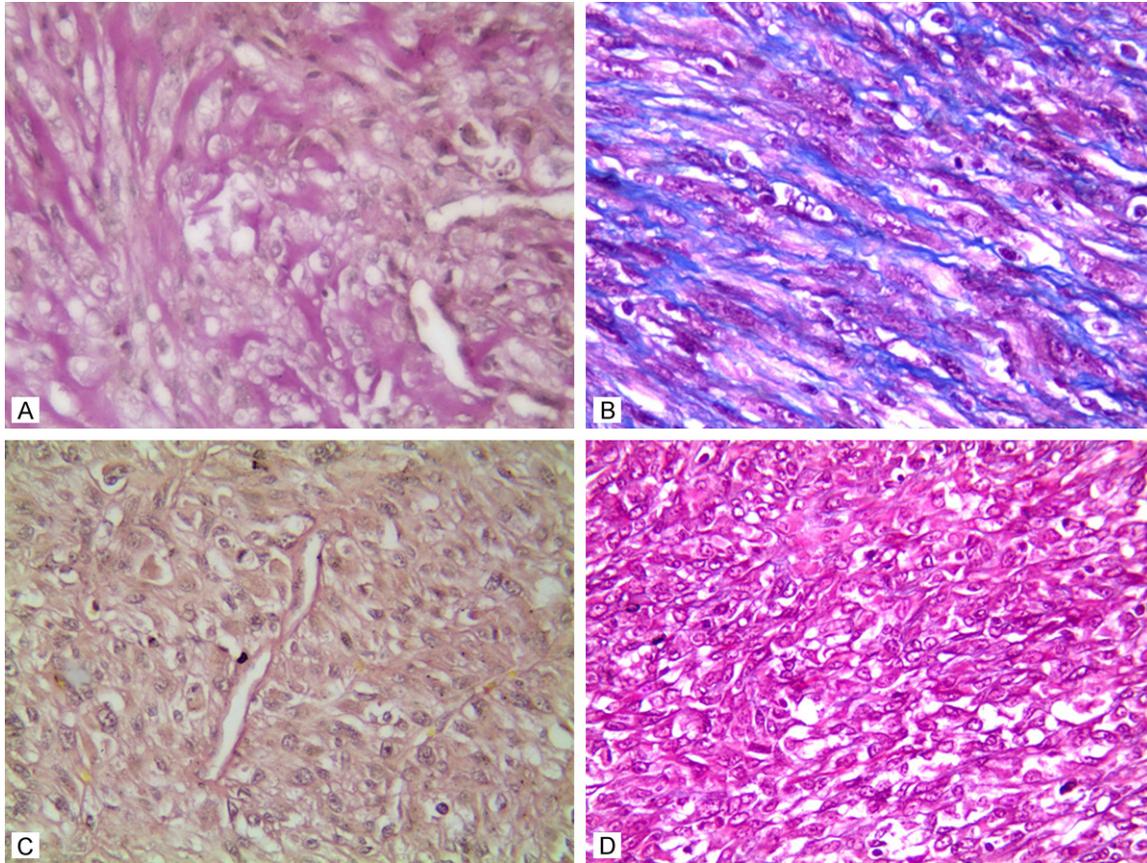


Figure 3. Histochemical staining of MS (Original magnification, $\times 400$). A. Tumor cells were in mixed color of red and yellow (VG staining). B. Tumor cells were in mixed color of blue and red (Masson's trichrome). C. Leiomyosarcoma were stained with yellow (VG staining). D. Leiomyosarcoma were stained with red (Masson's trichrome).

Table 3. Comparison of the partial clinicopathologic features of low grade and middle to high grade of MS

Clinicopathologic features	Low grade	Middle to high grade	P value
Number of cases	9	6	
Mean age \pm SD (years)	43.9 \pm 24.3	50.7 \pm 21.4	0.81
Mean tumor size \pm SD (cm)	2.7 \pm 1.1	7.8 \pm 2.7	0.03
Lymphocytes and plasma cells infiltration	5/9	3/6	0.71
Mean Mitotic count \pm SD (/10HPF)	1.9 \pm 0.8	6.2 \pm 1.2	<0.01
Mean Ki-67 index \pm SD (%)	6.0 \pm 2.2	20.0 \pm 7.1	<0.01
Recurrence and metastasis	1/8	4/6	0.09

The age of onset of MS has been reported to range from 6 to 75 years (mean age, 40 years), with a slight male predominance. MS is prone to occur in the soft tissues of the head and neck and in bone tissue [18-21], as well as in the limbs, chest wall, axillae, inguinal area, and abdominal/pelvic cavity. The tumors are located mostly in the deep soft tissues, especially in the muscle tissue, with some cases occurring in the superficial layers such as the subcutane-

ous or submucosal layer. The tumors are mostly solitary, and rarely present as multiple masses. A local painless mass is the most common clinical symptom, gradually developing over a period of 4 weeks to 72 months (mean, 13 months) [22, 23]. In this study, age and the location of the lesions were consistent with that in the literature.

In the previous studies, most tumor boundaries were not clear and showed infiltrative growth, while some tumors had clear boundaries but no capsule. Additionally, the tumors have been reported to be hard, contain a white section, and to be solid, with a diameter of 1.5-17.0 cm (mean, 3.14 cm). The tumor cells show intersected fasciculation and a vague storiform or swirled arrangement, and the tumor stroma is often accompanied by varying degrees of collagen fiber hyperplasia and hyaline degeneration, with dif-

Table 4. Comparisons of immunohistochemistry results among presently and previously reported cases of myofibroblastic sarcomas

Primary antibody	Present study (n=15)	Meng et al. [12] (n=20)	Montgomery et al. [9] (n=15)
Vimentin	15/15 (100%)	20/20 (100%)	15/15 (100%)
Smooth muscle actin	14/15 (93%)	18/20 (90%)	13/15 (87%)
Muscle-specific actin	12/15 (80%)	15/20 (75%)	7/9 (78%)
Calponin	10/15 (67%)	-	-
h-caldesmon	0/15 (0%)	0/20 (0%)	-
Fibronectin	15/15 (100%)	20/20 (100%)	-
Desmin	1/15 (7%)	2/20 (10%)	6/14 (43%)
ALK	0/15 (0%)	0/20 (0%)	-
CK	0/15 (0%)	-	0/15 (0%)
Laminin	0/15 (0%)	0/20 (0%)	-

ferent degrees of mucoid degeneration and inflammatory cell infiltration presented in some cases. Further, the tumor cells are spindle-, plump spindle-, or stellate-shaped, with abundant eosinophilic cytoplasm and no clear cell boundary, and spindle, oval, or slender wavy nuclei with small nucleolus are observed in some cases. The typical cell morphology was eosinophilic filamentous projections of one side of the cytoplasm, bending towards the nucleus. In addition, low-grade malignant cases have been reported to show mild nuclear atypia and a few mitotic figures, while moderate-to-high grade malignant cases show more atypia, hyperchromatic structures, obvious mitotic figures, central necrosis of the tumor, visible singular nucleation, and multinucleated giant cells. Some cases show diversity of the histological characteristics. In this study, we found that MS frequently exhibits a diverse histological appearance, which includes myxoid areas, hyalinization areas, and different degrees of inflammatory infiltration. In a few studies on pleomorphic malignant fibrous histiocytoma, some cases showed differentiation of myofibroblasts, accounting for an average of 3% (0-20%) of the total number of tumor cells. If the proportion of myofibroblasts is >30%, the lesion is regarded as high-grade MS [24, 25]. In the study, case 9 was diagnosed previously as a polymorphic sarcoma with myogenic differentiation, which accounts for more than 50% of the total number of tumor cells, it is now considered as high-grade MS.

Immunohistochemical studies have revealed that all, most, and few tumor cells stain positive

for vimentin and calponin, SMA, and desmin, respectively [9, 12, 26]. In addition, in the present study, the SMA in the tumor cells showed a linear enhancement pattern, and was found to localize in the cytoplasm around the membrane (**Figure 2C, 2D**), which differs from the cytoplasmic expression observed in tumors derived from smooth muscle cells, and which is consistent with electron microscopy findings of the cytoplasmic myofilament distribution of the two types of cells [9].

We furthermore examined the immunohistochemical features of MS herein, and found that FN was another important marker, while the tumor cells were negative for LN, an immunophenotype that is consistent with the ultrastructural features [12].

In one previous study, the proliferation index of Ki-67 was found to range roughly between 10-70%, and to vary according to the tumor grade and the different regions of the tumor. In this study, the Ki-67 index differed according to the grade, ranging 8-45%. Additionally, we found that Ki-67, a marker of proliferation, had a higher average labeling index in MS of moderate-to-high grade than that of low-grade MS.

From a literature review using the PubMed database, we found that the majority of reports on immunohistochemical staining of MS were single case reports. We compared the immunohistochemical staining results of our cases with those of two major case series in the English literature (Meng et al. [12]. and Montgomery et al. [9]; **Table 4**).

Moreover, some studies reported that VG and Masson histochemical staining is helpful for the diagnosis and differential diagnosis of MS [27]. Because myofibroblasts have characteristics of both smooth muscle cells and fibroblasts, the tumor cells show mixed colors of yellow and red or red and blue for the two kinds of staining methods, the proportions of which were found to be roughly equal. In the present study, after staining with VG and Masson's trichrome, we found that the respective ratios of yellow and red or red and blue were approximately 30-70% each. In the control group, the leiomyosarcoma tissues showed uniform red

and blue staining, respectively, while the fibrosarcomas showed uniform yellow and red staining, respectively, indicating that these two histochemical stains are helpful for the differential diagnosis of MS.

Most scholars consider that electron microscopy is the gold standard for the diagnosis of the presence of myofibroblasts. However, this method lacks practicality and its application is very difficult in routine clinical practice. Moreover, cells with the same morphology and cytoskeleton structure under the electron microscope may show heterogeneity in terms of the immunohistochemical phenotypes, and the fibronexus, a local specialized structure of the myofibroblasts, may be difficult to detect upon electron microscopic observation, owing to the loss and/or variability of their structural integrity during the process of tumor formation [22]. Thus, to a large extent, this has hindered our recognition of this disease entity and the accumulation of cases and experiences of this tumor. Nevertheless, some scholars claim that the correct diagnosis of MS can be made based on the morphological characteristics and relevant myogenic markers and histochemical findings [28].

Myofibroblasts are similar to fibroblasts and smooth muscle cells in morphology and show overlapping features in terms of the immunophenotype; accordingly, they are easily misdiagnosed, and the differential diagnosis is thus especially important. The following lesions should be considered in the differential diagnosis of MS: 1) Fibromatosis: the density of the tumor cells is relatively low, and it is characterized by a number of dense collagen fibers; polymorphism and nuclear polymorphism are not seen and positive myogenic marker expression is rare [21]. 2) Leiomyosarcoma: the tumor mainly exhibits a well-delineated pushing margin and generally lacks a diffusely infiltrative growth pattern; blunt nucleus ends with eosinophilic and longitudinally fibrillary cytoplasm are observed, and the tumor tissue is immunohistochemically positive for h-caldesmon [23]. 3) Malignant fibrous histiocytoma (MFH): this tumor mainly shows a woven or storiform arrangement, shows obvious polymorphism and atypia. Immunohistochemically, MFH frequently expresses CD68 and lysozyme and occasionally exhibits myoid phenotype focally. However, extensive expression of these markers can exclude the diagnosis of MFH [9]. 4) Fibrosarcoma:

abundant diffuse fasciculation of the cells is observed, and a dense and uniform, typical herring bone-like arrangement is noted; myogenic markers are negative [24]. 5) Malignant peripheral nerve sheath tumor: spindle tumor cells in a fascicular arrangement are observed. Typically, a cell-dense area and sparse area are visible, the stroma is delicate and uniform and the tumor cells are positive for S-100 protein and glial fibrillary acidic protein but negative for myogenic markers [17]. 6) Inflammatory myofibroblastic tumor (IMT): the tumor cell types and morphology are more diverse, and only some cases have clear clinical features; moreover, approximately half of all cases show positive ALK expression, while a subset is positive for CK. There is a partial overlap in the histological features and biological behavior of low-grade MS and IMT; however, we can differentiate the two according to the tumor growth pattern, cell density, cell purity, and cellular atypia, among other features [27].

Meng et al. [29] found, by comparative genomic hybridization detection, that the karyotype of tumorous myofibroblasts is complicated, with amplifications of chromosomes 1 P, 12 P, 5 P, and 22 P and the deletion of 15 q being the most frequent events in MS, and it is suggested that amplification of oncogenes and loss of tumor suppressor genes associated with the occurrence and development of this tumor may occur in these chromosomal regions. On the other hand, the ALK fusion gene was not detected, and its molecular pathogenesis may hence differ from that of IMT; instead, MS can be classified as a non-translocation related sarcoma.

Low-grade MS is, as the name suggests, a low-grade malignant tumor, which is prone to relapse but rarely metastasizes [30, 31]. On the other hand, moderate-to-high grade MS is not only associated with frequent relapses, but also with a high risk of metastasis [32, 33]. Chiller et al. [34] reported that the recurrence rate of this tumor was 44-75%, and that the metastasis rate was as high as 44%; these rates were all higher in moderate-to-high grade cases and there were even some mortality cases in their study. In particular, polymorphic MS is a highly malignant tumor, and its biological behavior is similar to those of other types of polymorphic sarcomas [24, 35]. As a general rule, surgical resection is the main means of treatment of MS; wide excision of the tumor

should be performed after the definitive diagnosis, and postoperative radiotherapy and chemotherapy should be supplemented depending on the final diagnosis and prognosis.

Conclusion

MS is a rare tumor, and its definition and characteristics are still controversial. As the number of studies on the topic is gradually increasing, the clinical features and malignancy degree of MS, and their relation with its histomorphology are becoming increasingly clear. All grades of MS should be included in the definition of this disease entity, however, the number of available cases is still low, and future studies with more cases are hence warranted in order to compare the findings and obtain more objective results.

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Disclosure of conflict of interest

None.

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