Myxofibrosarcoma: Cytomorphologic Findings and Differential Diagnosis on Fine Needle Aspiration

Matthew T. Olson^a Syed Z. Ali^{a, b}

Departments of ^aPathology and ^bRadiology, The Johns Hopkins Hospital, Baltimore, Md., USA

Key Words

Cytomorphologic findings • Fine needle aspiration • Histiocytoma • Malignant fibrous histiocytoma • Myxofibrosarcoma • Myxoid liposarcoma • Myxoid neoplasm • Soft tissue tumor

Abstract

Objective: To analyze the cytomorphologic findings of myxofibrosarcoma (MFS) on fine needle aspiration (FNA) and examine the differential diagnoses. **Study Design:** A retrospective review was undertaken of material from 22 patients with an FNA procedure of their tumor prior to resection. A tally was performed of all the features known in the literature, including myxoid matrix, spindle cells, nuclear pleomorphism, curvilinear vessels, and multinucleated cells. A review of the literature was also performed to elucidate any advances in the use of morphology and other modalities to deconvolute the challenging differential diagnosis. Clinicoradiologic characteristics and immunostaining were also analyzed and correlated. **Results:** FNA diagnoses included high-grade sarcoma (32%), recurrent MFS (23%), spindle cell neoplasm (18%), indeterminate-grade sarcoma (14%), low-grade sarcoma (9%), and pleomorphic adenoma (4%). Of the cases available for morphologic review, myxoid matrix was the most frequent observation (88%), followed by spindle cells (82%), nuclear pleomorphism (76%), multinucleated

cells (71%), and curvilinear vessels (65%). Myxoid matrix, spindle cells, and nuclear pleomorphism were very often concomitant observations. **Conclusion:** MFS demonstrates characteristic albeit nonspecific morphological findings and can overlap morphologically with other clinically significant entities based on FNA material.

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Introduction

Myxofibrosarcoma (MFS) [1] is a soft tissue sarcoma that typically presents on the extremities of adults in their 6th–8th decades. It has previously been called myxoid malignant fibrous histiocytoma (MFH) [2]. The MFS nomenclature now has broad consensus because of the reproducible morphologic appearance and ultrastructure [3]. MFS also portends a better prognosis than the variants of MFH [4–7]. MFS classically presents superficially in the lower extremities, followed by the trunk, upper extremities, neck, and head [1, 8–10], but it has also been reported superficially in the breast [11, 12], perineum [13], and orbit [14, 15]. Reports also exist of MFS in deep sites, including the esophagus [16], hypopharynx [17], vocal fold [18], parotid [19], heart [20–22], aorta [23], pulmonary artery [24], lung [25] and brain [26, 27].

While different schemes have been developed for grading MFS [9, 28, 29], there is agreement that the histologic grade is a predictor of metastatic potential [2] and worse survival [8]. Regardless of grade, resection is currently the mainstay of treatment for MFS. Adjuvant radiation plays a role at some institutions because of evidence that it reduces the risk of local recurrence [30, 31], although the published evidence is not unanimous [32, 33]. Reducing local recurrence is a clinically desired outcome both due to the morbidity reduction and the evidence that local recurrences may have a higher grade than the initial neoplasm [22, 34–36].

Because of the aggressive management options, the diagnosis of MFS with fine needle aspiration (FNA) – or at least the placement of the tumor into the spectrum of myxoid neoplasms – can direct the initial clinical treatment and follow-up, especially when the tumor involves the adjacent bone or joint [37]. Despite this need and the fact that MFS is one of the most common soft tissue sarcomas to present in late adulthood [30, 38], the cytopathologic features present on FNA have only rarely been described in case reports [11, 39] and two other institutional reviews consisting of 13 [40], 12 [41], and 6 [42, 43] patients. This work is a cytohistological correlation of 22 MFS patients seen at The Johns Hopkins Hospital, giving emphasis on cytologic features.

Methods

Specimen Identification and Cytopathology

All surgical resections over the last 30 years that were diagnosed as MFS or myxoid MFH were queried to find those cases for which an FNA was obtained prior to surgery. All FNAs were performed under ultrasound guidance with on-site evaluation by an attending cytopathologist or an experienced cytotechnologist. Direct smears were prepared in duplicate as material allowed; one smear was air dried and stained with DiffQuik, and the other was alcohol fixed and stained with the Papanicolaou stain. The median number of 3 passes took place during the FNA procedure (range 1–7), and this yielded a median of 3 DiffQuik- (range 0–7) and 2 Papanicolaou- (range 0–5) stained smears. A cell block was performed in 1 case, and paired core biopsies were performed in 5 cases. These cases were interpreted prospectively by 1 of 8 faculty members who are all board-certified cytopathologists.

Surgical Pathology

The resection specimens were sectioned and sampled in the standard fashion. They were diagnosed by a different group of pathologists than the cytopathologists who interpreted the FNA biopsies. Immunohistochemistry was not routinely performed on the resection specimens. Grading was assigned prospectively according to the National Cancer Institutes (NCI) grading scheme for soft tissue sarcomas [28].

Fig. 1. Radiographically, MFS is best visualized with MRI and typically has a nodular T₂-enhancing appearance. This view demonstrates MFS in the thigh.

Retrospective Review

Seventeen cases from the same number of patients were available for retrospective morphological review. The cases were reviewed looking for the classical features: spindle cells, multinucleate cells, myxoid background, nuclear pleomorphism, and curvilinear vascular structures. Each feature was scored for each case as either present or absent. The histopathology of the resection specimens was also reviewed.

Results

In our series, we identified 22 patients who had a final resection diagnosis of MFS and had undergone FNA prior to resection. The tumors were seen in both men ($n = 13$) and women ($n = 9$) with a male/female ratio of 1.4:1. The usual clinical manifestation was a painless incidentally discovered mass beneath the skin, although these tumors did present with pain in a subset ($n = 3$) of patients when the mass involved a joint or came into contact with clothing or sites of grooming. The age at first presentation ranged from 38 to 92 years (median 65 years). The demographics, cytologic diagnoses, and ultimate MFS grade from the resection are listed in table 1.

A representative cross-section of the radiology is shown in figure 1. The tumors in this series were best vi-

Fig. 2. Smears prepared from FNA of MFS typically show high cellularity at low power ($\times 10$, Papanicolaou stain).

sualized with magnetic resonance imaging (MRI) and were characterized as infiltrating and heterogeneously enhancing nodular septated masses with surrounding edema. The tumor was T₂ hyperintense with the T₁ signal usually isointense to muscle. The presenting greatest dimension ranged from 6 to 18 cm (median 14 cm), and the presenting tumor volume ranged from 100 to 1,600 cm³ (median 620 cm³).

The majority of MFS cases in this series were grades 2 and 3 on resection. Five (23%) of these cases were local recurrences; the primary tumors had been excised at other institutions. These cases were the only ones in which the specific diagnosis of MFS was made. Seven cases (32%) were diagnosed as 'high-grade sarcoma' on FNA, although 'spindle cell neoplasm' (18%), 'sarcoma' without a grade (14%), and 'low-grade sarcoma' (9%) were also used. Seventeen cases were available for morphological review, and a summary of the features demonstrated on review of the FNA material is given in table 2. Immunohistochemistry was performed on the FNA material of only 1 case. It was not immunoreactive for S100 protein or AE1/AE3.

In general, FNA from MFS was cellular on low power (fig. 2). The most prominent features included myxoid matrix (fig. 3), spindle cells, nuclear pleomorphism (fig. 4), multinucleated cells (fig. 5), and curvilinear vascular structures (fig. 6). Myxoid material is prominent in 88%; its absence had the tendency to discourage the placement of the tumor into the realm of myxoid neoplasms unless the patient had a known history of MFS. Our mor-

Table 1. Demographics, body site, grade, and FNA interpretation for 22 MFS cases

Age	Sex	Location	FNA	Grade
51	M	thigh	LGS	1
81	M	cervical spine	PA	1
47	F	calf	UGS	2
50	F	thigh	HGS	2
50	F	thigh	HGS	2
50	M	axilla	SCN	2
51	M	calf	MFS	2
56	F	forearm	UGS	2
56	F	thigh	UGS	2
61	M	thigh	SCN	2
63	M	calf	HGS	2
67	F	calf	MFS	2
69	F	thigh	HGS	2
68	M	thigh	MFS	2
78	M	lumbar spine	LGS	2
82	M	calf	HGS	2
38	F	chest wall	SCN	3
67	M	calf	MFS	3
67	M	prostate	MFS	3
73	F	thigh	SCN	3
78	M	thigh	HGS	3
92	M	forearm	HGS	3

LGS = Low-grade sarcoma; PA = pleomorphic adenoma; UGS = ungraded sarcoma; HGS = high-grade sarcoma; SCN = spindle cell neoplasm; MFS = recurrent MFS.

Table 2. Counts listed for the morphological features in the 17 cases of MFS available for morphological review

Feature	Cases, n
Myxoid matrix	15 (88%)
Spindle cells	14 (82%)
Nuclear pleomorphism	13 (76%)
Multinucleated cells	12 (71%)
Curvilinear vessels	11 (65%)

phological examination has revealed 12 cases with abundant large multinucleated cells. This review contains a predominance of grades 2 and 3 MFS, so the finding of multinucleated cells is somewhat expected. Review of the 2 cases of grade 1 MFS failed to show multinucleated cells. Conversely, all cases of grade 3 and 80% of grade 2 MFS showed numerous multinucleated cells.

Given the high percentage of cases that contained more than one feature, the number of coexistent features as well as specific features that occurred together was

Fig. 3. When it is present, the myxoid matrix from MFS is usually copious ($\times 10$, DiffQuik stain).

Fig. 4. MFS often demonstrates a spectrum of nuclear shapes ranging from spindle-shaped to ovoid ($\times 20$, Papanicolaou stain).

Fig. 5. Multinucleated cells are a common finding in MFS ($\times 40$, Papanicolaou stain).

Fig. 6. The curvilinear blood vessels in MFS can be present as small segments or, as in this case, in large fragments ($\times 10$, Papanicolaou stain).

examined (fig. 7). Interestingly, only 1 case demonstrated spindle cells alone, and this had been called ‘spindle cell neoplasm’ at the time of sign-out. The case that demonstrated only 2 features was erroneously diagnosed as ‘pleomorphic adenoma’ due to its placement in the upper neck. The majority of cases demonstrated three or more of the classic but nonspecific features. Not surprisingly, when the findings were examined for specific features

that demonstrated concomitant observations (fig. 7b), the typical image emerged of a smear with myxoid matrix, nuclear pleomorphism, and spindle cells. Spindle cells had a high level of co-observation with both nuclear pleomorphism and multinucleated cells. Interestingly, the two least frequent observations – multinucleated cells and curvilinear vessels – had a very high rate of co-observation.

Fig. 7. The number of the five MFS features (myxoid matrix, spindle cells, nuclear pleomorphism, curvilinear vessels, and multinucleated cells) that was observed in the FNA cases is plotted in **a**. Co-observation of two features is plotted in **b**. More co-observed features have darker intersections.

Fig. 8. Gross cross-section of the resection specimen. The tumor is invading the vastus lateralis muscle.

Fig. 9. Histopathology from a low-grade MFS resection specimen with myxoid matrix and predominantly spindle-shaped cells with some epithelioid cells. Curvilinear vascular structures can also be seen in this field.

Upon resection, the gross appearances of these tumors were described as heterogeneous and nodular with variable and scattered pockets of grossly apparent matrix. A representative cross-section from a resection of MFS in the vastus lateralis is shown in figure 8. Histologically, MFS resections demonstrated all of the features that were

apparent on cytopathology – including curvilinear vessels, spindle cells, nuclear pleomorphism, and myxoid matrix. An example of the histology seen in a low-grade MFS is shown in figure 9.

Differential Diagnosis

The myxoid variant of nodular fasciitis (MNF) [44] is an important diagnostic consideration because it is benign and often self-limiting, so does not always require excision [45]. The morphologic overlap between MNF and MFS can be high because both demonstrate myxoid matrix, spindle cells, and a high degree of anisonucleosis. To aid in distinguishing these two lesions, MNF is a faster growing lesion, so it typically presents with pain at a smaller size. Additionally, the nuclei of MNF usually have prominent nucleoli, and the mitotic rate is higher in MNF than in MFS [46]. If it is possible, immunohistochemistry can be useful since the MNF labels with stains for smooth muscle actin and histiocyte markers, while MFS has not been shown to do this [47].

The distinction between MFS and myxoid liposarcoma (MLS) is clinically useful because MLS is susceptible to traditional and experimental chemotherapeutic regimens [48, 49]. This is often difficult on FNA material alone. In an FNA study on MLS [50], cytologic preparations of this tumor were found to contain a less prominent vascular network and vacuolization in the tissue fragments. MLS also demonstrates more cellular uniformity. The cellular uniformity in MLS is the most important feature as it is commensurate with the observation that MLS is associated with translocations: primarily the t(12;16)(q13;p11) translocation [51–53] and less commonly the t(12;22)(q13;q12) translocation [54, 55]. MFS is not associated with clonal translocations [56, 57]; some tumors even have normal karyotypes [36].

Because of the similarity in nomenclature and occasionally overlapping histological appearance, MFS can be confused with low-grade fibromyxoid sarcoma (LGFMS) [58, 59]. MFS and LGFMS differ epidemiologically; LGFMS typically presents 10–20 years earlier than MFS, which classically presents in the 6th–8th decades. These entities can often be separated morphologically because LGFMS is poorly vascularized, so does not typically exhibit curvilinear vessels. Additionally, the nuclei of LGFMS are not as pleomorphic as those of MFS [60]. There is a paucity of solid qualitative immunohistochemical differences between these two entities [9, 61]. While one publication demonstrates quantitative immunohistochemical differences in cell cycle markers between these two tumors [10], the practical use of these for distinguishing between LGFMS and MFS – especially on cytologic preparations – is dubious. LGFMS is associated with the t(7;16)(q34;p11) translocation [62], which has not been shown in MFS [63]. Another translocation-associ-

ated sarcoma, extraskeletal myxoid chondrosarcoma (EMCS), is often separated from MFS with light microscopy alone because of the arrangement of EMCS cells into cohesive cords and the characteristic lacunar appearance. EMCS has stereotyped cytogenetic translocations; classically EMCS harbors t(9;22)(q22;q12) [64, 65], although t(9;17)(q22;q11) [66] and t(9;15)(q22;q21) [67] have also been reported. Although very rare, chordoma periphericum can be placed in the differential diagnosis as it contains myxoid matrix [40, 68]. The physaliferous cells arranged in chords and immunoreactivity for cytokeratin stains are helpful features in making this diagnosis and distinguishing it from MFS.

Intramuscular myxoma (IM) is a diagnostic consideration. The two entities can be difficult to separate with FNA based on morphology alone [69]. As MFS can invade muscle, and myxoma can spread superficially, location is not always helpful in separating these two entities [70]. Histologically, IM is a poorly vascularized tumor as opposed to MFS, in which the curvilinear vasculature is often prominent. The distinction is important because IM has a benign natural history with a low risk for recurrence and metastasis [71]. Molecular analyses have shown that IM – but not MFS – harbors the activating missense *GNAS1* mutation on codon 201 [72, 73], although the data about the diagnostic value of this mutation are currently inadequate. Myxoid neurofibroma is another consideration. Morphologically, myxoid neurofibroma has collagen fibrils intermixed with the spindle cells and should have less nuclear pleomorphism than MFS. If it is possible, immunohistochemistry is helpful in making this distinction as myxoid neurofibroma labels with the immunohistochemical stain for S100 protein [74]. Myoepithelial tumors of soft tissue can have the same clinical presentation as MFS. Cytopathologic and histopathologic division of these two entities can be challenging as they both exhibit variable amounts of myxoid matrix, pleomorphic epithelioid cells, and spindle cells. Myoepithelial tumors of soft tissue can demonstrate other epithelial or metaplastic features, such as ducts, clear cells, or cartilage, and when these are present they are helpful. Myoepithelial tumors of soft tissue are immunohistochemically distinct from MFS. They are particularly immunoreactive for cytokeratins, S100 protein, and calponin [75].

Vascular tumors with myxoid features, such as pleomorphic hyalinizing angiectatic tumor, and angiomyxoma can present subcutaneously and in the same anatomical distribution as MFS. Histological overlap including myxoid material and variable nuclear pleomorphism can lead to diagnostic confusion with pleomorphic hyalin-

izing angiectatic tumor [76–78]. The classic features supporting the latter diagnosis, such as extensive hyalinization, vascular ectasia, and hemosiderin-laden macrophages are nonspecific. Furthermore, it is not clear from the literature or our experience how well the vascular hyalinization or ectasia would be appreciated on FNA material. Similarly, the curvilinear blood vessels and myxoid material can also lead to confusion with angiomyxolipoma [79] and angiomyxoma [80, 81]. The lipid droplets in angiomyxolipoma could be helpful in supporting this diagnosis. Angiomyxoma tends to have more vascular telangiectasia and less morphological heterogeneity than MFS. While immunohistochemical data in all of these contexts are lacking, it seems reasonable that a lack of CD34 staining in the neoplastic cells would support the diagnosis of MFS.

High-grade MFS can overlap morphologically with spindle cell melanoma [82], but immunohistochemistry for any of the melanoma markers would provide resolution. When the MFS is of high grade, it is often not possible to separate it from pleomorphic sarcoma because both these entities demonstrate high cellularity, a high degree of nuclear pleomorphism, and generally low amounts of myxoid material [43, 83]. There is usually not a consequence to making this distinction with current management options [84]. When it is present, myxoid matrix is a helpful cue that the tumor is a high-grade MFS. However, as little as 10% of sections from a high-grade MFS may show myxoid matrix [9, 85]. This is a relevant detail in two commonly encountered clinical scenarios. First, MFS commonly presents at a high grade, and the myxoid matrix may not be sampled with the FNA procedure. Second, in the FNA of recurrent MFS, lack of myxoid matrix is perfectly consistent with a recurrence given that the grade often advances, and high-grade tumors have low amounts of matrix.

Discussion

The diagnostic sensitivity of prominent myxoid material for making the classification of a myxoid neoplasm on FNA material is dubious based on these data given the observation that only 88% of our cases demonstrated prominent myxoid material. In several cases, the myxoid stroma was very thin and difficult to appreciate. The 2 cases that did not show myxoid material were both of high grade on resection. This finding agrees with previous investigations that have linked scant myxoid matrix with a higher grade.

Three entities that demonstrate substantial morphological overlap with MFS – MLS, EMCS, and LGFMS – are translocation-associated sarcomas. A fluorescent *in situ* hybridization probe has been developed [86] that detects the most common translocations associated with these tumors, and this was deployed retrospectively in a small number of tumors with success. It remains to be demonstrated if these translocations are beneficial in prospective diagnostic analysis. If such an approach does lead to a clinically useable assay, MFS would be a genetic diagnosis of exclusion with the current available research because it is too complex to categorize with translocations or single mutations. In other developments, one investigator has used mass spectrometry and immunohistochemistry to detect differences in the specific collagen and proteoglycan composition of the extracellular matrices of EMCS and MFS [87] as well as IM and MFS [73]. While these data are preliminary, their potential for offering a secondary means of categorizing myxoid tumors is significant [88]. It remains to be demonstrated if these same changes are common for large numbers of tumors or if the same tools can be used to differentiate MFS from other myxoid tumors and if this approach is robust in prospective diagnostic endeavors.

The use of FNA for soft tissue neoplasms varies significantly among institutions. As the procedure is inexpensive and carries little risk, it has been shown to carry some desirable features as a first-line diagnostic modality for assessing lesions of this type [43]. The two major drawbacks are the difficulty in separating MFS from other myxoid neoplasms and the inability of FNA material to provide a grade for MFS. As discussed, the myxoid neoplasms demonstrate different morphological features, but these are nonspecific; morphology can only take the diagnosis so far. Indeed, as our own data show, the specific diagnosis of MFS was only made in cases of local recurrence. However, given recent advances in the cytogenetic and molecular understanding of the other myxoid tumors, FNA appears more ideally suited than ever as a diagnostic modality for myxoid neoplasms. While a clinical trial has yet to be performed, one could envision a practice whereby on-site evaluation was used to direct the appropriate complement of molecular and biochemical assays that could rapidly lead to the correct diagnosis and follow-up management. The challenge of deciphering a high-grade MFS from pleomorphic sarcoma is one that is not likely to be resolved without further advances in molecular diagnostics, but this distinction would be difficult to make on core biopsy and would lead to the same management: resec-

tion. Thus, this ambiguity in the diagnosis need not be a deterrent for pursuing FNA in the workup of a soft tissue tumor.

Conclusion

In conclusion, FNA interpretation of myxofibrosarcoma can be challenging since the cytopathologic findings overlap those of numerous other entities. However, the

placement of the tumor into the spectrum of myxoid neoplasm is realistic with the morphologic findings. Advances in the molecular characterization of myxoid neoplasms appear to provide the necessary specificity to distinguish between the entities within the differential diagnosis. If the combination between morphology and molecular methods accomplishes this task, FNA could provide the ideal diagnostic procedure for the initial workup of soft tissue neoplasms.

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