Myxoinflammatory Fibroblastic Sarcoma

Review and Update

David R. Lucas, MD

Myxoinflammatory fibroblastic sarcoma is a rare soft tissue tumor with most occurring in the distal extremities of adult patients. It has a high rate of local recurrence and a low rate of metastasis. Because it may appear benign on clinical examination, and because the microscopic features are generally underrecognized, it is often inadequately treated and misdiagnosed. In this review, based upon experience and that of the literature, the intent is to highlight salient clinicopathologic features, detail the broad microscopic spectrum including high-grade aggressive variants, review the molecular features, and discuss its relation to hemosiderotic fibrolipomatous tumor.

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BACKGROUND

Myxoinflammatory fibroblastic sarcoma (MIFS) is a rare soft tissue tumor first reported in 1998 by 3 independent investigators. Montgomery et al1 described 51 cases that they called inflammatory myxohyaline tumor of distal extremities with virocyte or Reed-Sternberg-like cells. They observed neoplastic cells with large, inclusion-like nucleoli within a myxoid and fibroinflammatory milieu, frequent involvement of the hands and feet, and potential for local recurrence. Meis-Kindblom and Kindblom2 reported 44 cases as “acral myxoinflammatory fibroblastic sarcoma,” which mostly involved distal extremity sites, had a high rate of local recurrence, and metastasized to a regional lymph node in 1 case, the first documentation of its metastatic potential. Finally, Michal3 reported 5 cases in the hand called inflammatory myxoid tumor of the soft parts with bizarre giant cells, none of which recurred. Because it is now known to occur in both acral and nonacral body sites, the World Health Organization has retained but modified Meis-Kindblom’s original appellation by dropping the term acral.

To date more than 400 cases of MIFS have been reported including a large cohort of 104 cases4 along with descriptions of high-grade, aggressive variants.5,6

EPIDEMIOLOGY AND CLINICAL FEATURES

Myxoinflammatory fibroblastic sarcoma presents as a painless, slowly growing mass. It typically affects adult patients with an average age around 40 years. However, the age range is broad and includes both young children and nonagenarians. The sex ratio is 1:1. It has a distinct propensity for acral and dorsal4 soft tissue locations, especially finger, hand, wrist, foot, and ankle, which together account for two-thirds of cases.7 The dorsal foot/anterior ankle region is a characteristic site. However, MIFS can occur at various body sites including proximal extremities, trunk, and head and neck.

Clinically, MIFS may resemble a benign lesion such as synovitis, ganglion cyst, or tenosynovial giant cell tumor. Elongated, fusiform growth can mimic an inflammatory condition. Because of its oftentimes benign clinical appearance, it is often treated inadequately at first surgical operation. By imaging, MIFS typically presents as a diffusely enhancing, lobulated, subcutaneous mass with nonspecific magnetic resonance imaging features suggestive of either a benign or malignant process.8,9 Association with tendons and deep/intramuscular localization is not uncommon. Rare tumors invade bone,6,8 or destroy a joint, mimicking osteomyelitis or arthritis.8

PATHOLOGY

Grossly, MIFS is lobulated and varies from gelatinous to fleshy to firm, often being heterogeneous in color and texture (Figure 1). It usually occurs in subcutaneous adipose tissue where it infiltrates along fibrous septa and fascial planes. The average size is 3 cm; however, large progressive tumors measuring up to 30 cm have been reported.9 Its broad histologic spectrum presents a major diagnostic challenge. For example, the proportions of myxoid lobules (Figures 2 and 3), fibroinflammatory areas (Figures 4 and 5), and cellular areas vary greatly from case to case, as do the numbers of cells with inclusion-like nuclei (Figure 6) often regarded as the hallmark cell of MIFS. Another diagnostic challenge is presence of a heavy inflammatory infiltrate that obscures the neoplastic cells (Figure 4).

The spectrum of neoplastic cells found in MIFS varies within and among tumors. In addition to large histiocytoid or ganglion-like cells with inclusion-like nucleoli, there are...
spindle cells with fibrillary cytoplasm (Figure 7), large epithelioid cells with abundant eosinophilic cytoplasm (Figure 8), degenerated cells with smudged chromatin (Figure 9), neoplastic cells filled with mucoid vacuoles, so-called pseudolipoblasts found within myxoid areas (Figure 10), and large histiocytoid cells with emperipolesis, usually containing intracytoplasmic neutrophils (Figure 11).

Within myxoid lobules, the neoplastic spindle and epithelioid cells often interconnect with one another to form strands, complex networks (Figure 12), and dis cohesive sheets (Figure 13) forming a so-called dilapidated brick wall pattern. The inflammatory infiltrate usually consists of lymphocytes and lymphoid aggregates. However, substantial numbers of neutrophils, eosinophils, macrophages, and plasma cells are often present. The mitotic rate is generally low and necrosis is uncommon. The importance of correctly diagnosing MIFS is that it can be mistaken for either an inflammatory process or another malignant tumor such as Hodgkin lymphoma or a more aggressive sarcoma such as myxofibrosarcoma. As summarized by Jeremia and Thway, immunohistochemistry plays a very limited role in the diagnosis of MIFS, since there are no specific diagnostic markers.

Recently, high-grade examples of MIFS have been reported. These include cellular tumors with increased mitotic rates, atypical mitoses, or necrosis (Figure 14), and dedifferentiated tumors that show abrupt transition from low-grade MIFS to an undifferentiated pleomorphic sarcoma phenotype (Figure 15, A and B). In a series of high-grade MIFSs, Michal et al. reported 18 patients with available follow-up. Nine (50%) developed metastases, including 7 who died. Most tumors in this series were situated in proximal locations with only 1 tumor in a distal extremity. One breast tumor occurred post radiation. The median age was higher than in conventional MIFS (66 years compared to 40 years), and the average size was larger (8.3 cm compared to 3.0 cm).

**GENETIC FINDINGS**

The first description of cytogenetic findings in MIFS was by Lambert et al. in 2001 who reported a complex karyotype with reciprocal t(1;10)(p22;q24) and loss of...
In some tumors the fibroinflammatory areas have dense hyalinizing fibrosis (hematoxylin-eosin, original magnification ×400).

Histiocytoid cells with large, vesicular nuclei and “inclusion-like” nucleoli that mimic Reed-Sternberg cells are characteristic of myxoinflammatory fibroblastic sarcoma and can be found in most tumors (hematoxylin-eosin, original magnification ×600).

Spindle cell areas are common in myxoinflammatory fibroblastic sarcoma, consisting of cells with plump, elongated nuclei and fibrillary eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×400).

Some myxoinflammatory fibroblastic sarcomas are dominated by very large epithelioid cells with abundant eosinophilic cytoplasm and eccentric nuclei (hematoxylin-eosin, original magnification ×400).

Cells with degenerated (“smudged”) chromatin are common in myxoinflammatory fibroblastic sarcoma (hematoxylin-eosin, original magnification ×400).

The myxoid areas in myxoinflammatory fibroblastic sarcoma frequently contain “pseudolipoblasts.” The cytoplasm in such cells is distended by vacuoles filled with myxoid matrix (hematoxylin-eosin, original magnification ×200).
Figure 11. Emperipolesis may be seen in myxoinflammatory fibroblastic sarcoma, consisting of large histiocytoid cells engulfing inflammatory cells, usually neutrophils (hematoxylin-eosin, original magnification ×600).

Figure 12. In the myxoid areas, spindle cells can interconnect to form a reticular pattern (hematoxylin-eosin, original magnification ×200).

Figure 13. Loosely cohesive epithelioid cells separated by extracellular myxoid matrix are present in this myxoinflammatory fibroblastic sarcoma (hematoxylin-eosin, original magnification ×200).

Figure 14. High-grade features can be seen in myxoinflammatory fibroblastic sarcoma such as marked nuclear pleomorphism and brisk mitotic activity as shown, as well as areas of necrosis. Note the loosely cohesive cellular pattern and myxoid background (hematoxylin-eosin, original magnification ×200).

Figure 15. This tumor shows sharp demarcation between conventional low-grade myxoinflammatory fibroblastic sarcoma consisting of scattered neoplastic cells within an inflammatory fibromyxoid background with arrow indicating a neoplastic cell with inclusion-like nucleolus (A), and high-grade undifferentiated sarcoma with fascicles of pleomorphic spindle cells, brisk mitotic activity, and atypical mitoses (B) (hematoxylin-eosin, original magnification ×400 [A and B]).
chromosomes 3 and 13. Reciprocal t(1;10) was similarly reported in a hemisiderotic fibrolipomatous tumor (HFLT),\(^\text{11}\) as was a report of a hybrid MIFS/HFLT with der(10)(t(1;10)),\(^\text{12}\) suggesting a close relationship between these 2 neoplasms. These findings in addition to shared epidemiologic features such as mid-adult age, acral location (especially ankle, foot, and leg), and tendency for local recurrence supported the notion that HFLT and MIFS were related entities.

Hallor et al\(^\text{13}\) studying 8 MIFSs identified 2 genetic pathways. In one pathway they mapped breakpoints in t(1;10) to TGFB3 in 1p22 and MGEA5 in 10q24 that resulted in upregulation of NPM3 and FGFR8, both located close to MGEA5. They also noted that no fusion product was formed by this translocation because the 2 components were transcribed in opposite directions, thus no functional gene could be created. For the second pathway they identified a ring chromosome with a commonly amplified gene could be created. For the second pathway they identified a ring chromosome with a commonly amplified gene. For the second pathway they identified a ring chromosome with a commonly amplified chromosome 3 and 13. Reciprocal t(1;10) was similarly reported in a hemisiderotic fibrolipomatous tumor (HFLT),\(^\text{11}\) as was a report of a hybrid MIFS/HFLT with der(10)(t(1;10)),\(^\text{12}\) suggesting a close relationship between these 2 neoplasms. These findings in addition to shared epidemiologic features such as mid-adult age, acral location (especially ankle, foot, and leg), and tendency for local recurrence supported the notion that HFLT and MIFS were related entities.

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Antonescu et al,\(^\text{14}\) studying 7 MIFSs, 14 HFTLs, and 3 hybrid tumors, found rearrangements of TGFB3 and MGEA5 in 83% of cases, including all 3 hybrid tumors. They also identified amplification of VGLL3 in 10 of 12 cases in both MIFS and HFLT. They concluded that MIFS and HFLT shared a pathogenetic relationship and they were either different morphologic variants or different levels of tumor progression of a single biologic entity.

Not all cases of MIFS, however, have t(1;10) or ring chromosomes, and instead show other genetic alterations. Recently, Zreik et al\(^\text{15}\) reported data indicating most MIFSs actually lack these genetic findings. Using fluorescence in situ hybridization probes to detect rearrangements of TGFB3 and MGEA5 in 31 pure MIFSs, 8 hybrid tumors, 2 pleomorphic hyalinizing angiectatic tumors (PHATs), and 2 HFTLs, they observed that TGFB3 and MGEA5 rearrangements were largely limited to hybrid HFLT-MIFS (6 of 8 cases), PHAT, and HFLT, and only rarely detected in pure MIFS. Only 2 of 31 pure MIFSs had MGEA5 rearrangement and none had TGFB3 rearrangement. The authors concluded that TGFB3 and MGEA5 rearrangements are much more common in hybrid HFLT-MIFS tumors than in classic MIFS, that HFLT and pure MIFS are unrelated, and that hybrid HFLT-MIFS tumors most likely represent HFLT with sarcomatous progression rather than a neoplasm strictly related to MIFS. Such variances in results and conclusions among investigators indicate that the final word regarding the molecular genetic classification of MIFS is not out.

**PROGNOSIS AND TREATMENT**

Myxoinflammatory fibroblastic sarcoma is locally aggressive. It recurs 22% to 67% of the time, yet metastasizes in only 2% of cases, mostly to regional lymph nodes. However, pulmonary and widespread metastases do occur. Atypical histologic features\(^\text{4}\) and high-grade histology\(^\text{5}\) have been implicated as negative prognostic indicators. Myxoinflammatory fibroblastic sarcoma is best treated by complete surgical excision, while radiation has been associated with improved local control.\(^\text{16}\)

**CONCLUSIONS**

Myxoinflammatory fibroblastic sarcoma is a rare soft tissue sarcoma that tends to occur in the distal extremities in adults patients. It may be mistaken for an inflammatory process on clinical grounds and is often undertreated. Its heterogeneous histologic findings and high inflammatory background make the diagnosis challenging for pathologists. In general, MIFS has a high potential for local recurrence and low potential for metastasis, consistent with a low-grade sarcoma. Recently however, high-grade, aggressive variants have been reported. As discussed above, the molecular findings are inconsistent, yet there appears to be a close relation with HFLT in some, but not all, MIFSs. Additional clinicopathologic and molecular studies should help to further define the spectrum and classification of this tumor.

**References**

1. Montgomery EA, Devaney KO, Giordano TJ, Weiss SW. Inflammatory myxohyaline tumor of distal extremities with vireocyte or Reed-Sternberg-like cells: a distinctive lesion with features simulating inflammatory conditions, Hodgkin’s disease, and various sarcomas. Mod Pathol. 1998;11(4):384–391.
2. Meis-Kindblom JM, Kindblom LG. Acral myxoinflammatory fibroblastic sarcoma: a low-grade tumor of the hands and feet. Am J Surg Pathol. 1998;22(8):911–924.
3. Michal M. Inflammatory myoid tumor of the soft parts with bizarre giant cells. Pathol Res Pract. 1998;194(8):529–533.
4. Laskin WB, Fetisch JF, Miettinen M. Myxoinflammatory fibroblastic sarcoma: a clinicopathologic analysis of 104 cases, with emphasis on predictors of outcome. Am J Surg Pathol. 2014;38(1):1–12.
5. Michal M, Kazakov DV, Hradkowsky L, Kinkor K, Kuroda N, Michal M. High-grade myxoinflammatory fibroblastic sarcoma: a report of 23 cases. Ann Diag Pathol. 2015;19(3):157–163.
6. Gaetke-Udager K, Yablonski CM, Lucas DR, Morag Y. Myxoinflammatory fibroblastic sarcoma: spectrum of disease and imaging presentation. Skeletal Radiol. 2016;45(3):347–356.
7. Lombardi R, Jovine E, Zannini N, et al. A case of lung metastasis in myxoinflammatory fibroblastic sarcoma: a clinicopathological study. Br J Cancer. 2014;110(2):410–415.
8. Kumar R, Lefkowitz RA, Neto AD. Myxoinflammatory fibroblastic sarcoma: clinical, imaging, management and outcome in 29 patients. J Comput Assist Tomogr. 2016;41(1):104–115.
9. Jeremias E, Thway K. Myxoinflammatory fibroblastic sarcoma: morphologic and genetic updates. Arch Pathol Lab Med. 2014;138(10):1406–1411.
10. Lambert I, Debrie-Rychter M, Guelinckx P, Hagemeijer A, Sciot R. Acral myxoinflammatory fibroblastic sarcoma with unique clonal chromosomal changes. Virchows Arch. 2001;438(5):509–512.
11. Wettach GR, Boyd LJ, Lawce HJ, Magenis RE, Mansoor A. Cytogenetic analysis of a hemisiderotic fibrolipomatous tumor. Cancer Genet Cytogenet. 2008;182(2):140–143.
12. Fico CP, Martino-Enriquez A, Abraham JA, Dal Cin P, Hornick JL. Hybrid myxoinflammatory fibroblastic sarcoma/hemosiderotic fibrolipomatous tumor: report of a case providing further evidence for a pathogenetic link. Am J Surg Pathol. 2010;34(11):1723–1727.
13. Hallor KH, Sciot R, Staal J, et al. Two genetic pathways, t(1;10) and amplification of 3p11-12, in myxoinflammatory fibroblastic sarcoma, haemosiderotic fibrolipomatous tumour, and morphologically similar lesions. J Pathol. 2009;217(3):716–727.
14. Antonescu CR, Zhang L, Nielsen GP, Rosenberg AE, Dal Cin P, Fletcher CD. Consistent t(1;10) with rearrangements of TGFB3 and MGEA5 in both myxoinflammatory fibroblastic sarcoma and hemosiderotic fibrolipomatous tumor. Genes Chromosomes Cancer. 2011;50(10):757–764.
15. Zreik RT, Carter JM, Sukov WR, et al. TGFB3 and MGEA5 rearrangements are much more common in “hybrid” hemosiderotic fibrolipomatous tumor–myxoinflammatory fibroblastic sarcomas than in classical myxoinflammatory fibroblastic sarcomas: a morphological and fluorescence in situ hybridization study. Hum Pathol. 2016;53:14–24.
16. Tejwani A, Kokayashi W, Chen YL, et al. Management of acral myxoinflammatory fibroblastic sarcoma. Cancer. 2010;116(24):5731–5739.