



Myxoinflammatory Fibroblastic Soft Tissue Sarcoma with Multiple Recurrences, Case Report of Uncommon Tumor with Challenging Diagnosis and Review of the Literature

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Abstract

Myxoinflammatory fibroblastic soft tissue sarcomas are rare soft tissue sarcomas predominantly found in the upper extremities of middle-aged adults. Their rarity and diverse histological and anatomical presentations predispose to misdiagnosis oftentimes for more benign lesions such as ganglion cyst, giant cell tumor of the tendon sheath or tenosynovitis. This results in improper management in addition to delayed diagnosis placing patients at increased risk of worst-case scenarios including amputation, metastases or death. We are presenting the case of a 5-year-old female with myxoinflammatory fibroblastic soft tissue sarcoma of her hand initially misdiagnosed as a ganglion cyst, that recurred on two occasions after undergoing local excision. The reporting of this case aims to increase knowledge and awareness regarding the morphologic and immunohistochemical features of rare and often misdiagnosed myxoinflammatory fibroblastic soft tissue sarcomas. It is our hope that heightened awareness of this tumor will lead to inclusions as a differential diagnosis in soft tissue lesions of the extremities and thus avoid misdiagnosis and treatment.

Keywords: Fibroblastic, Myxoid, Myxoinflammatory, Sarcoma, Recurrence

ABBREVIATION

MIFS: Myxoinflammatory fibroblastic sarcoma, **TGCT:** Tenosynovial giant cell tumor, **HFLT:** Hemosiderotic fibrohistiocytic lipomatous tumor

INTRODUCTION

Soft tissue sarcomas are considerably rare as they account for approximately 1% of adult malignancies¹⁻³. They are characterized as being both histologically and anatomically diverse. Myxoinflammatory fibroblastic sarcoma (MIFS) is a low-grade sarcoma that is locally aggressive with rare distant metastases. It was first described in the literature by Meis-Kindblom and Kindblom in 1998⁴. Although initially believed to be predominantly found in acral sites, it is now understood that these tumors may arise elsewhere and is thus now classified by

the WHO as myxoinflammatory fibroblastic sarcoma^{5,6}. MIFS is a rare neoplasm with less than 200 reported cases⁵. Interestingly, there is a wide age variability of presentation, with most cases occurring in the fourth and fifth decades of life. There have also been documented cases in children and those in their 10th decade of life⁵. The lesion typically presents as a painless mass in the distal extremities⁷ that exhibits slow growth but often infiltrates the surrounding soft tissues⁷. Due to its slow growth and painless features, the differential diagnoses are mostly composed of benign entities. These include but are not limited to ganglion cysts, giant cell tumors and tenosynovitis⁵. Due to their rarity, specialist physicians are typically not well acquainted with the diagnostic suspicion and appropriate treatment for these scarce cases. The lack of commonplace of these cases as well as the broad degree of benign differential diagnoses increase the propensity of physicians to misdiagnose and mismanage a potentially severe disease, that may in some instances lead to grave consequences such as amputation, metastases or death. We present the case of a 5-year-old girl with myxoinflammatory fibroblastic sarcoma of her hand initially misdiagnosed as a ganglion cyst, that recurred on two occasions after undergoing local excision.

CASE PRESENTATION

A 5-years-old girl presented with a firm, painless mass in her left hand that appeared over several months, and recently increased in size. The mass measured 3.2 cm located at the dorsal aspect of the base of left 3rd metacarpal bone and initially considered to be a Ganglion cyst. Coronal T1-weighted MR image showed ovoid mass on third interdigital space that was slightly hypointense to skeletal muscle. The mass showed complete peripheral isointense rim. The mass was surgically excised with

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clear safe surgical margins. The excised tumor was described as multinodular tan-white mass with gelatinous areas alternating with firm white areas suggestive of myxoid and fibrotic tumor.

Pathological microscopic examination showed multinodular lesion composed of variable myxoid and fibrous hyalinized areas with associated dense inflammatory infiltrate (**Figure 1A**). Tumor cell population was composed of epithelioid to spindled cells with scattered large cells showing bizarre nuclei and prominent nucleoli resembling viral inclusions or Reed-Sternberg cells (**Figure 1B**). Many cells showed epithelioid, lipoblast-like and ganglion-like cells in myxoid background (**Figure 1C & 1E**). Moderate atypia was noted, but only few scattered mitosis less than 2/10HPF. Tumor cells were negative for Cytokeratin AE1/AE3, LCA, Melan-A, CD15, CD30 and Synaptophysin. The tumor cells were positive for Vimentin, BCL-2, CD 68, and Factor XIIIa. The tumor cells were focally positive for S-100 and Desmin. The immunohistochemistry profile was non-specific, but with the clinical presentation and characteristic morphologic features, a diagnosis of Myxoinflammatory Fibroblastic Sarcoma was rendered. No postoperative treatment was provided.

Two years later, recurrent tumor appeared at the same site. The patient underwent local excision with pathological evaluation showing recurrent myxoinflammatory fibroblastic sarcoma measuring 2.7 cm in size, with extension to the deep margin and a close 1 mm anterior margin. A definitive clear margin was not

possible. The recurrent tumor showed more atypical nuclear features and increased mitotic activity exceeding 5/10HPF. A metastatic workup including CT scans of the chest, abdomen, and pelvis revealed no evidence for metastatic progression of the tumor. Nine months later, a new mass appeared at the edge of the prior surgical scar. After multidisciplinary tumor board discussion, it was decided to treat the patient with preoperative radiation therapy, followed by surgical excision due to the recurrent nature of the patient's disease. The excised tumor showed same features as the prior recurrence.

Patient was followed up for 6 years with no evidence of metastasis or recurrence, after which she was lost to follow up

DISCUSSION

Myxoinflammatory fibroblastic sarcoma (MIFS) is a rare soft tissue sarcoma that was first reported by Meis-Kindblom and Kindblom in 1998¹. It is a rare neoplasm with less than 200 reported cases⁵. The tumor presents as a painless, slowly growing mass found two thirds of the time in acral soft tissue locations including the finger, hand, foot, wrist and ankle⁸. A large study discovered that MIFS of distal acral sites was more commonly found on dorsal soft tissue⁹ and that most patients report evidence of the lesion less than one year before clinical intervention occurs⁹. MIFS was shown to have the highest incidence in the fourth and fifth decades of life, but there are

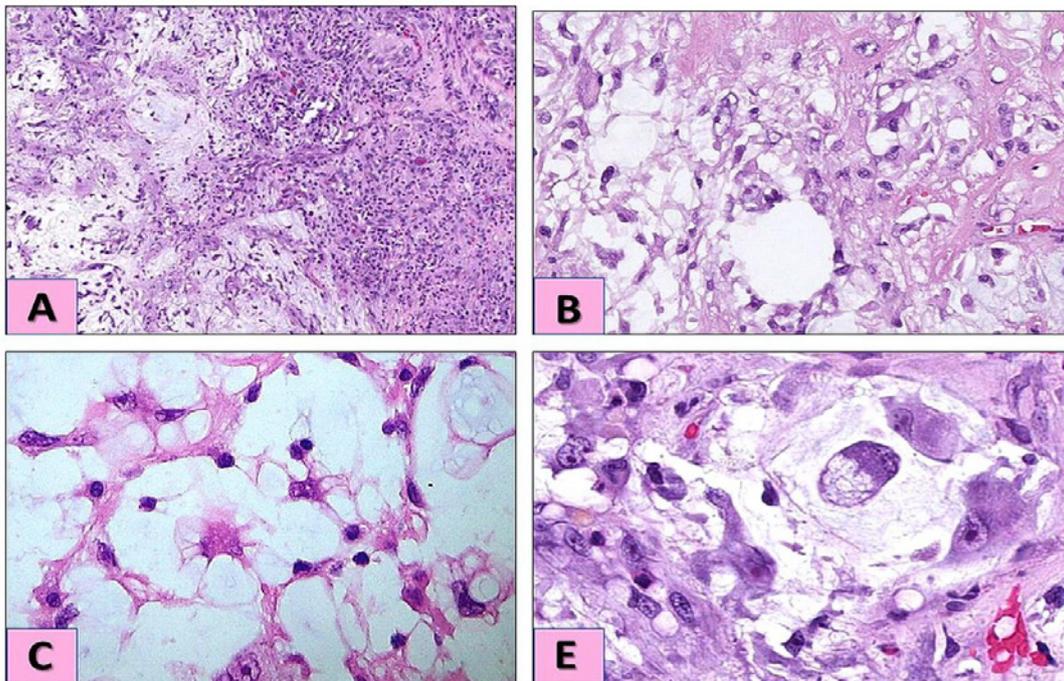


Figure 1 Histopathologic examination of the tumor

Figure 1A: Multinodular lesion composed of variable myxoid and fibrous hyalinized areas with associated dense inflammatory infiltrate (H&E stain X20).

Figure 1B: Tumor cell population composed of epithelioid to spindled cells with scattered large cells showing bizarre nuclei and prominent nucleoli resembling viral inclusions or Reed-Sternberg cells (H&E stain X40).

Figure 1C & 1E: Many cells show epithelioid, lipoblast-like and ganglion-like cells in myxoid background (H&E stain X60)..



also documented cases in children, like our presented case and those in their 10th decade of life⁵. It does not display a gender predominance⁸. This tumor is unique in that it customarily resembles common benign lesions such as tenosynovial giant cell tumor (TGCT), ganglion cyst or synovitis⁸. Furthermore, its propensity to exhibit fusiform and elongated growth may be confused for an inflammatory lesion⁸.

The differential diagnosis for lesions presenting similar to MIFS is dependent upon the histologic predominance of each tumor component⁵. Predominance of inflammatory infiltrate with associated low cellularity may mimic an infectious or inflammatory lesion⁵. However, infectious lesions are typically associated with lymphadenopathy and show microbial infection⁵. A myxoma may be suspected in variants of MIFS that exhibit few cells⁵. Myxomas are characterized by spindle to stellate cells with bland nuclei and long cytoplasmic processes and lack ganglion-like cells and inflammatory factors⁵. Diffuse-type TGCT is often found in joints and is composed of bland mononucleated ovoid cells that lack atypia, with hemosiderin deposition and inflammatory cells consisting of lymphoplasmacytic cells and histiocytes⁵. TGCT lacks the presence of eosinophils, neutrophils, myxoid centers and large, atypical neoplastic cells⁵. The differential diagnosis of acral soft tissue spindle cell lesions also includes fibrohistiocytic lipomatous tumor particularly because cases may have mixed characteristics of hemosiderotic fibrohistiocytic lipomatous tumor (HFLT) and MIFS⁵. Of note, a t(1;10) translocation has been detected in both MIFS and HFLT cells⁵. In our case, clinical presentation alone led to the initial diagnosis of ganglion cyst, as it was located on the dorsal aspect of the hand and painless.

Although the benign mimics of MIFS are more common in differential diagnoses, malignant lesions should also be considered⁵. Malignant mimics are composed of significant myxoid components⁵. Myxofibrosarcoma and MIFS are similar in that they exhibit nodularity, pseudolipoblasts and myxoid stroma⁵. However, myxofibrosarcoma predominantly presents in the acral locations of older patients and is composed of an extensive vascular network with minor inflammatory constituents⁵. Extranodal Hodgkin lymphoma may be considered in the differential diagnosis of MIFS due to the presence of virocyte-like cells⁵. However, Hodgkin lymphoma does not exhibit myxoid foci and lacks the presence of neutrophils⁵. Moreover, Reed Sternberg cells found in HL express both CD15 and CD30 whereas the fibroblastic cells of MIFS do not express either of these CD markers⁵.

On gross inspection, MIFS appears as gray-white to yellow with a firm to myxoid consistency most commonly found subcutaneously with involvement of the dermis⁵. It is known to invade surrounding structures including fascia, tendons, ligaments and muscle⁵. Under the microscope, the tumor is composed of zones of basophilic myxoid material interspersed within fibrohyaline and focally hemorrhagic stroma⁵. It also consists of acute and chronic inflammatory cells namely, eosinophils, neutrophils, lymphocytes and plasma cells with three distinct types of neoplastic cells⁵. The first neoplastic cells are spindle to epithelioid that exhibit moderate nuclear atypia⁵.

The second type of neoplastic cell are large, atypical epithelioid ganglion-like cells that appear similar to Reed-Sternberg cells and virocytes⁵. These cells are composed of large eosinophilic nucleoli, vesicular nuclei and vast amphophilic cytoplasm⁵. The third type are pseudolipoblast cells that are described as atypical cells with compressed nuclei and excess vacuolated myxoid basophilic cytoplasm containing mucous material⁵. Of note, the amount of inflammatory infiltrate can vary widely and, in some cases, may obscure the population of neoplastic cells, mimicking a lymph node⁵. Contrarily, the cellularity of the tumor may be limited causing the tumor to resemble a myxoma⁵.

MIFS is both diffusely and robustly positive for vimentin and focally positive for CD68⁵. The KI-67 proliferation index typically labels less than 10% of cells⁵. It shows variable expression of epithelial membrane antigen, smooth muscle actin, calponin, factor XIIIa, CD34 and cytokeratin⁵. Notably, it is variably reactive to CD163, CD117, α 1-antitrypsin and EGFR⁵. MIFS is almost always negative for markers including CD30, CD15, HMB-45, Melan-A, desmin, GFAP, CAM 5.2, CD45 and neuron specific enolase⁵. Although virocyte-like cells are often found in these tumors, immunohistochemical and histochemical staining for bacteria, fungi, mycobacteria, CMV and HSV is persistently negative⁵. It has been documented that the origin of the tumor stems from fibroblast cells that are rich in intermediate filaments, mitochondria and rough endoplasmic reticulum⁵.

MIFS is a low-grade malignant neoplasm that involves two distinct genetic pathways with the first being a reciprocal translocation t(1;10)(p22;q24) and the second being amplification of genetic material on chromosome 3⁵. The t(1;10) translocation results in an increased expression of FGF8 that is involved in cell growth, morphogenesis, tumor growth and invasion⁵. The second distinct genetic pathway involving amplification of a small segment on ring chromosome 3 results in overexpression of both VGLL3 and CHMP2B genes with the VGLL3 gene playing a role in regulating transcription⁵.

On magnetic resonance images, MIFS appears as a multinodule, poorly circumscribed mass with extensive involvement of the tendon sheath¹⁰. The involvement of the tendon sheath often mimics that seen on MRI in tenosynovitis¹⁰. However, tenosynovitis can be differentiated from MIFS with visualization of accumulation of fluid with increased signal intensity of the affected tendon on T2 weighted MR images¹⁰. Additionally, clinically, tenosynovitis often decreases in size over time whereas MIFS is known to slowly grow and infiltrate surrounding tissues over time¹⁰. In MRI images with low signal intensity on T1-weighted images and high signal on T2-weighted images, MIFS has a signal intensity similar to that of a cyst¹¹. To appreciate the solid nature of the lesion, contrast enhanced T1-weighted images are more accurate¹¹. T2-weighted images demonstrate heterogeneous hyperintensity with focal zones of hypointensity and wide involvement of tendons which may cause misdiagnosis of giant cell tumor of the tendon sheath¹¹. Notably, MRI is not able to differentiate MIFS from close mimics such as giant cell tumors of the tendon sheath, acral fibromyxoma, myxoid liposarcoma or myxofibrosarcoma¹⁰.



Due to the rarity of this tumor, there currently lacks a definitive treatment regimen. However, the knowledge that this tumor frequently invades surrounding structures such as tendon sheaths, fascia, ligaments and muscle suggest that these nearby structures cannot be saved during excision¹. The original report of MIFS by Meis-Kindblom and Kindblom demonstrated that 67% of cases developed local recurrence after undergoing excision and 28% of these cases required amputation for definitive treatment, particularly in those that experienced multiple recurrences⁴. Although seemingly rare (6%), metastases have been reported to regional lymph nodes, the lung and the skull¹. In the limited literature discussing MIFS, the consensus is that wide resection of the lesion is the treatment of choice due to the high rate of recurrence¹¹. After wide excision, physical examinations should be performed 4 times a year for the first 2 years, and then every 6 months up to 5 years to inspect for local or regional tumor metastases¹¹. In some instances, it may be necessary to order a chest x-ray to examine for distant disease if clinical suspicion arises for lung involvement¹¹.

In cases of MIFS, it is difficult to obtain wide margins on surgical excision due to the level of local infiltration of the tumor and propensity of upper extremity involvement⁷. A review by Tejwani et al. examined the management of MIFS in 17 patients⁷. They found that of the 5 patients that had positive surgical margins and that underwent preoperative RT and an intraoperative or postoperative RT boost, all were free of local or distant disease at the time of their last follow-up⁷. This suggests that in the future, RT may be implemented to maintain local control in patients that have positive margins after surgical excision⁷. It may also provide physicians with the ability to preserve function of the nearby structures while sustaining local control⁷.

AMFS is a rare sarcoma that is frequently initially misdiagnosed as a benign lesion leading to suboptimal management and delay in the appropriate treatment course. Due to the possibility of metastasis, although rare, this tumor should be included in the differential diagnosis of slow growing painless masses of the hand in order to provide optimal diagnosis and management.

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