



Low Grade Myofibroblastic Sarcoma of the Bone with Recurrence as a High Grade Sarcoma: Case Report and Review of the Literature

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Abstract

High-grade myofibroblastic sarcoma (HGMS) is a rare malignancy characterized by a high rate of recurrence and metastasis. This form of malignancy tends to be indolent in nature and patients' initial complaints are usually a painless mass. In this report, we present a case of a 40-year-old male who was initially evaluated for a left knee mass. Imaging studies and biopsy evaluation concluded the diagnosis of low-grade myofibroblastic sarcoma of the distal femur and surrounding soft tissue. Despite adherence to current treatment standards for this particular malignancy, the patient experienced recurrence requiring further surgical intervention, adjuvant chemotherapy and radiotherapy. Recurrent tumor was in the form of high-grade myofibroblastic sarcoma. After exhausting all available treatment options, the patient expired secondary to multi-organ failure associated with widespread metastases. In this report, we discuss how to differentiate this sarcoma from other types of sarcomas and provide a brief review of the literature.

Keywords: Myofibroblastic; Low grade; High grade; Recurrence; Chemotherapy

Abbreviation

LGMS: Low grade myofibroblastic sarcoma, **HGMS:** High-grade myofibroblastic sarcoma, **MS:** Myofibroblastic sarcomas, **IMT:** Inflammatory myofibroblastic tumor, **IHC:** Immunohistochemistry, **MFH:** malignant fibrous histiocytoma

Introduction

Myofibroblastic sarcomas (MS) are rare malignancies that have been better understood over the last few years; however, clearly defined diagnostic criteria have not been well developed (1). Myofibroblasts are defined as modified fibroblasts that are short, bi-or tripolar spindle-shaped or stellate cells, with a single, small, wavy or ovoid pale-staining nucleus with only a small amount of cytoplasm. Myofibroblasts have a contractile element and can synthesize collagens and other stromal components, including fibronectin and laminin. They are naturally part of the stroma of various tissues, including testicular peritubular stroma, the periodontal ligament, as well as inflammatory and reparative granulation tissue; however, they are also the principal cell type in some reactive and neoplastic soft-tissue

lesions (2). These neoplasms, termed myofibroblastic sarcomas, are rare and typically originate throughout the body including the head, neck extremities and trunk and are classified based on their morphological characteristics into low, intermediate, and high grade (3).

The current classification system for myofibroblastic sarcomas can be regarded as low, intermediate, and high-grade (4). Low grade myofibroblastic sarcoma (LGMS) are infiltrative tumors, usually located within deep soft tissue, and have a predilection for the head and neck region. These tumors display varied microscopic appearances, from fasciitis-like to fibrosarcoma-like, but they all, at least focally, display nuclear pleomorphism (3). However, no recurrent cytogenetic or molecular markers have been described thus far (5). LGMS express smooth-muscle actin and calponin, some express desmin, and most lack h-caldesmon. These sarcomas can recur but rarely metastasize. Inflammatory myofibroblastic tumor (IMT) and infantile fibrosarcomas can be regarded as two additional LGMS, which are usually seen in younger patients. IMTs typically arise in locations including the lung, retroperitoneum or mesentery (3). LGMS invade locally and are known to progress to high-grade sarcoma (6).

LGMS are distinct from High-grade myofibroblastic sarcoma (HGMS), also called pleomorphic myofibrosarcoma, which are malignant fibrous histiocytoma (MFH)-like tumors. These are more frequently Actin positive than other MFH tumors (3). HGMS is diagnosed by cytomorphological analysis and immunohistochemistry (IHC) studies and has higher recurrence and metastatic rates than low-grade myofibroblastic sarcoma (7). A study of HGMS found that 29% of these tumors recurred, 71% metastasized, and 43% of patients died of disease. When compared with undifferentiated pleomorphic sarcomas, HGMS differentiation has better prognosis. Still, HGMS is a more aggressive tumor and has a worse prognosis than LGMS (3).

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Case Presentation

A 40-year-old man with a prior history significant for mild hypercholesterolemia managed with medication presented with a left knee mass. Imaging studies revealed a large, infiltrating mass involving the distal left femur and surrounding soft tissue measuring 5.5 x 3 cm that was highly suspicious for sarcoma. Biopsy of the mass showed bundles of spindle cells arranged in a fascicular and storiform growth patterns in background of variable stromal collagen with prominent hyalinization and numerous thin walled capillaries (**Figure 1A-B**). The tumor displayed infiltrative borders and tumor cells showed ill-defined pale eosinophilic cytoplasm, fusiform elongated and wavy nuclei, evenly distributed chromatin with indentations and small nucleoli (**Figure 1C**). With IHC studies, these cells were SMA and desmin positive and negative for h-caldesmon, ALK, and CD34. Pathologic examination was consistent with the diagnosis of Low grade myofibroblastic sarcoma.

The patient received Neoadjuvant chemotherapy and 6 months later, the entire tumor was removed with total knee replacement. Viable non-necrotic tumor represented 40% of the resected tumor mass which included the distal femur, proximal tibia, knee joint, and surrounding soft tissue excision.

After post-surgery adjuvant chemotherapy, the patient remained in remission and free of recurrence or metastasis for two and half years. This was until the patient presented with a large left thigh mass proximal to the knee replacement measuring 4.8 cm x 3.2 cm. Neoadjuvant chemotherapy was initiated followed by above left knee amputation and the mass was excised.

The tumor was markedly pleomorphic compared to the original sclerotic low grade sarcoma resected two years earlier (**Figure 2A**). Marked cellular atypia was noted with prominent necrosis and mitotic activity exceeding 20 mitosis/10HPF (**Figure 2B**). The tumor showed minimal response to chemotherapy with less than 10% tumor death in the form of necrosis (the necrotic

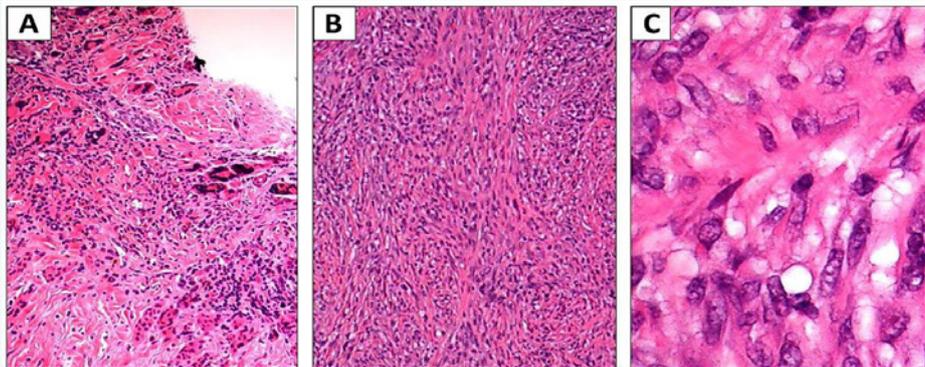


Figure 1 Microscopic features of low grade myofibroblastic sarcoma (Initial tumor)

1A: The tumor displayed infiltrative borders (H&E stain X20)

1B: Bundles of spindle cells arranged in a fascicular and storiform growth patterns in background of variable stromal collagen (H&E stain X40)

1C: Tumor cells showed ill-defined pale eosinophilic cytoplasm, fusiform elongated and wavy nuclei, evenly distributed chromatin with indentations and small nucleoli. Significant atypia is minimal (H&E stain X60).

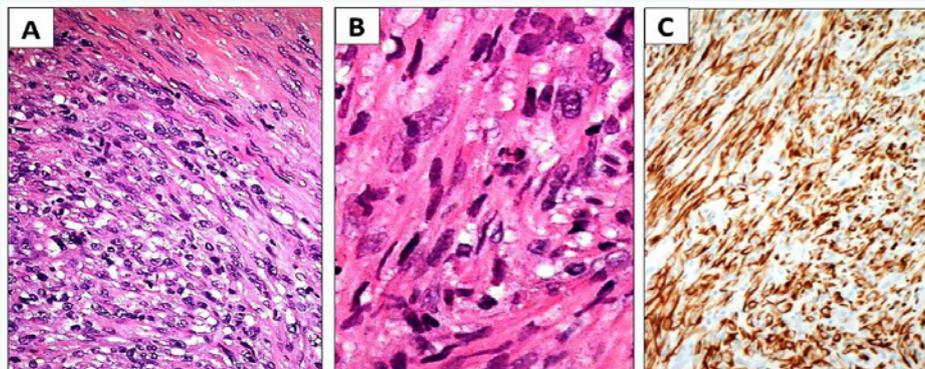


Figure 2 Microscopic features of High grade myofibroblastic sarcoma (Recurrent tumor)

2A: Tumor is markedly atypically cellular than the original sclerotic low grade sarcoma (H&E stain X40).

2B: Marked cellular atypia with pleomorphism, hyperchromasia, prominent nucleoli and increased mitotic activity (H&E stain X60).

2C: Tumor cells positive for Desmin.



tumor in the original low grade sarcoma was 60%). This resistant response to chemotherapy may be an indication that the tumor is more aggressive, reflecting the high grade nature of the tumor. IHC studies were performed on the viable tumor tissue and reported as follow: Positive staining was obtained for Vimentin, α -SMA, desmin (**Figure 2C**), h-caldesmon, CK AE1/AE3, laminin, S100 (focal), and CD34. High proliferation was noted with 25% nuclear staining with Ki-67. The tumor cells were reported negative for Pan Melanoma markers.

The histomorphology together with the immunohistochemistry studies, though not completely specific, were consistent with recurrent myofibroblastic sarcoma now with high grade features. Six months following this procedure the patient expired with widespread metastasis and multiple organ failure.

Discussion

High-grade myofibroblastic sarcoma is a rare malignancy with high recurrence and metastatic rates (7). Diagnosis of myofibroblastic sarcoma is typically done with histomorphologic features aided by IHC studies. This is also the best way to differentiate between HGMS and LGMS. HGMS is usually immunopositive for Alpha- smooth muscle actin (α -SMA), muscle-specific actin, vimentin, and fibronectin, and is occasionally positive for desmin. Further, it is immunonegative for h-caldesmon, CK, laminin, S100, and CD34 (7). Of these, α -SMA appears to be the best immunohistochemical marker for identifying differentiated myofibroblasts. However, even α -SMA specific immunohistochemical staining is not able to fully distinguish the various cellular elements within smooth muscle. These methods of immunohistochemical staining only apply to fully differentiated cells. As such, they are not a good marker for tumor grading. (8). Myofibroblastic differentiation seen in HGMS can also be visualized on electron microscopy (3).

Myofibrosarcomas (MS) should be distinguished from leiomyosarcoma, IMT, fibromatosis, and nodular fasciitis. It is not uncommon for MS to bear resemblance to leiomyosarcoma under light microscopy. In particular, under microscopy, leiomyosarcomas typically exhibit a well delineated pushing margin, generally lack a diffusely infiltrative growth pattern, and often show more eosinophilic and longitudinally fibrillar cytoplasm and cigar-shaped vesicular nuclei with perinuclear vacuolation. In contrast MS has spindle-shaped cells exhibiting an indistinct and paler cytoplasm which is less fibrillary than that in leiomyosarcoma and have a tapering rather than blunt-ended nucleus with common infiltration of inflammatory cells in the stroma. (9) Similar differentiations must be made for IMT, fibromatosis, and nodular fasciitis as it is important for prognosis and treatment consideration. Nevertheless, myofibroblastic differentiation in pleomorphic sarcomas cannot be used as a favorable prognostic indicator. (3)

There are no standard guidelines for the treatment of HGMS, as it is a rare malignant tumor, and there is limited clinical information on the outcomes of nonsurgical treatments, such as chemotherapy and radiation therapy. However, currently, the

most effective definitive treatment for MS is surgical excision with wide margins (7). Generally, a margin of at least 1-2 cm is recommended because microscopically positive surgical margins are associated with a high risk of local recurrence, distant metastasis and death. (10) Still, given the lack of treatment guidelines, adjuvant therapies, including chemotherapy and radiotherapy, are also often implemented (7). Meng et al suggested management based on grading. Grade 1 MS are locally aggressive lesions with frequent recurrence, so management by wide excision of the tumors with long-term follow-up is suggested. Grade 2 MS exhibit higher recurrence rates and frequent metastasis. These should be managed by excision with a wide margin of normal tissue and adjuvant radiation therapy or systemic chemotherapy (9). The patient in our case received 6 months of neoadjuvant chemotherapy prior to surgical excision and adjuvant therapy. This combination achieved two and a half years of remission, but eventually ended up with recurrence and ultimately, the patient succumbed to the disease. Here we see various approaches to HGMS treatment, none of which have achieved a consistently high level of success; often subsequently, resulting in significant morbidity and mortality.

While tumor grade is important, tumor location, size, growth pattern, and operative treatment methods used are also significant factors for determining MS recurrence and prognosis (4). Meng et al. conducted a study of 20 cases which indicated that MS had a higher recurrence rate in the bone than that in other locations (9). Similarly, in our case, the patient's tumor was located in the distal femur and recurred multiple times.

This case highlights the limited bank of knowledge regarding myofibroblastic sarcoma and its treatment. Even with proper diagnosis, treatment and follow up, complete remission is often not achieved. It is our hope that this report raises awareness of including high-grade myofibroblastic sarcoma in the differential diagnosis of soft tissue masses presenting in the extremities. We also hope that this report will raise the awareness of what remains an unmet need in definitive management of this type of uncommon sarcoma and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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