Biology, Classification, and Management of Recurrent Myxofibrosarcoma 21 Years After Resection

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Abstract

Soft-tissue sarcomas (STSs) are a heterogenous group of rare malignancies that have significant lifelong implications. Accepted management options include limb-sparing surgical resection and adjuvant radiation therapy.

Here we present the case of a myxoid malignant fibrous histiocytoma, now termed a myxofibrosarcoma, which recurred 21 years after primary surgical resection. To our knowledge, this is the longest documented interval between initial management and recurrence of an STS.

Significant changes have been made in classification guidelines and diagnostic methods over this 2-decade period. The pathogenesis of remote recurrence of STSs remains controversial and is discussed in this report.

Extremity soft-tissue sarcomas (STSs) are a group of rare tumors that account for less than 1% of all malignancies that arise annually in the United States.[1] These sarcomas are often characterized by local aggressiveness and formation of a pseudocapsule with a propensity for metastasis to the lungs. Current management regimens involve taking a multidisciplinary approach to the patient—surgical resection, perioperative radiation therapy for local control, and chemotherapy for control of systemic disease.[2-4] Most cases of local recurrence come within 2 years of primary tumor resection.[5,6]

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In this article, we present the case of myxofibrosarcoma, previously termed a myxoid malignant fibrous histiocytoma,which recurred 21 years after primary surgical resection without adjuvant therapy. To our knowledge, this is the longest documented interval between initial management and recurrence of an STS. The potential for remote recurrence should be considered during long-term postoperative management of myxofibrosarcomas. We also describe classification and management of STSs as well as possible mechanisms for remote recurrence.

The patient provided written informed consent for print and electronic publication of this case report.

Case Report

A 78-year-old white man presented to our institution for evaluation of a soft-tissue mass on the left elbow. The mass was less than 3 cm from a 1985 tumor resection site. The earlier tumor was diagnosed as a malignant fibrous histiocytoma (MFH), myxoid variant, and was definitively managed with a wide surgical resection, which achieved disease-free margins.

The patient discovered the recent mass, painless and progressively enlarging, 2 months before presenting to us. He denied shortness of breath, coughing, and other pulmonary symptoms. Physical examination of

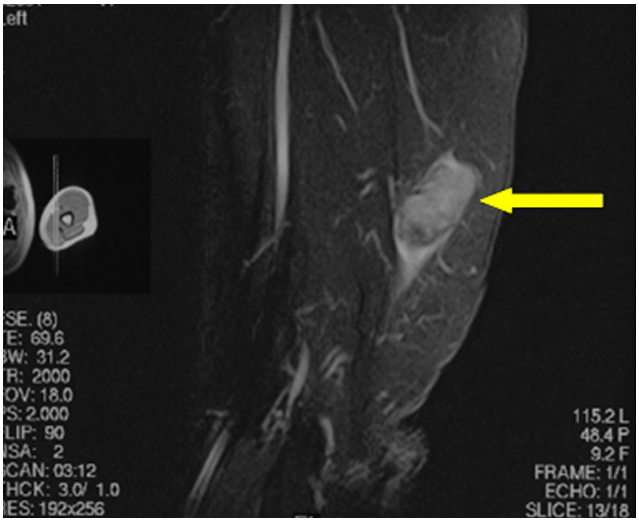

Figure. Magnetic resonance imaging (short tau inversion recovery sequence) shows enhanced, heterogenous signal of lesion in left arm.

the left upper extremity revealed a well-healed surgical site, which included a split-thickness skin graft over the lateral epicondyle of the left elbow (Figure). A palpable soft-tissue mass, 2 cm in its longest dimension, was appreciated in the subcutaneous tissue just proximal to the surgical bed. This mass demonstrated no tenderness or overlying cutaneous changes. The patient could fully mobilize the elbow without difficulty or pain.

Plain radiographs showed soft-tissue fullness on the lateral aspect of the arm, consistent with the location of the previous tumor and the physical examination. No intralesional mineralization was appreciated. Magnetic resonance imaging (MRI) showed an encapsulated 2×2-cm lesion just beneath the subcutaneous tissues, 6 cm proximal to the lateral epicondyle. The lesion exhibited enhanced T_2 signal on short tau inversion recovery sequence (Figure). Given the patient's significant past history, and the location and recent clinical and radiologic appearance of the lesion, we recommended an excisional biopsy.

The biopsy was performed, and histologically wide negative margins were obtained. The closest margin, at the inferior aspect of the lesion, measured 2 cm. The mass was grayish-tan, had areas of hemorrhagic necrosis, and measured 2.2×1.5×1.3 cm. Immunohistochemical staining revealed pleomorphic, spindled tumor cells positive for vimentin and negative for actin, desmin, CD34, and pancytokeratin. An S-100 stain produced weak, nonspecific, cytoplasmic staining. Pathologic analysis was compatible with the diagnosis of a high-grade myxofibrosarcoma. The surgical margins were microscopically free of malignant cells.

The patient returned home the day of surgery, and his recovery was unremarkable. The wound healed completely and without complication. The patient has been followed up every 4 months to 6 months for 36 months, and there has been no local or distant recurrence on physical examination, serial MRI of the upper extremity, or computed tomography (CT) of the chest.

Discussion

A pathologic description of MFH, a member of a subgroup of STSs, was provided by Ozzello and colleagues[7] in 1963. MFH was described histologically as consisting of fibroblastic spindle cells, polygonal histiocytic cells, and giant cells. Cellular etiogenesis has been attributed to histiocytic precursors.[8] Electron microscopy, immunohistochemistry, and molecular genetics have surpassed previous morphologic methods of classification and have given us a better understanding of this pathologic entity.[9-11] In 2002, the World Health Organization reclassified MFH into specific sarcomas and declared MFH and undifferentiated pleomorphic sarcoma (UPS) synonymous.[12] UPS is now defined as a UPS subtype for which all modes of pathologic identification have proved unsuccessful.[13] Before reclassification, MFH was considered the most common sarcoma, representing approximately 40% of adult mesenchymal malignancies.[13] This inaccuracy was largely caused by the antiquated classification schema encompassing a large heterogenous group of pathologies on the basis of histologic characteristics. This led to overapplication of the diagnosis and provided the impression of a higher incidence of disease. UPS better classifies this group of undifferentiated tumors, accounting for less than 5% of all adult STSs diagnosed annually.[12]

We believe that our patient's extremity STS is evidence of recurrent disease and not a separate presentation of a primary tumor. A potential criticism of this report is that the initial tumor and "recurrence" were not tested (by genetic or immunohistochemical analysis), so we do not truly know if they were identical. Separate tumors arising from the scar tissue of perisurgical beds after tumor resection have been reported before and are attributed to individual patient genetic susceptibility, chronic tissue inflammation, and long-term biological reparative processes.[14-17] In our patient's case, the likelihood that his most recent tumor was a distinct primary lesion is low, given the identical histologic description of the 2 pathologies. The initial tumor had been described as consisting of malignant myxoid and fibrous cells—matching the current description of myxofibrosarcoma.[13,18] Also, the recurrent lesion was confirmed with immunohistochemical and genetic analysis to be a myxofibrosarcoma. Given the histologic similarities and proximity of these tumors, we propose that the most recent lesion can be accurately identified as recurrent disease.

The reason for the 2-decade interval between our patient's initial presentation and tumor recurrence is unclear. One answer might involve an association between local recurrence and disease-related mortality—an association that continues to be debated. Some authors have supported the idea that local recurrence predicts metastatic disease and, ultimately, disease-related mortality.[19-24] However, evidence also supports a noncausal relationship.[25-29] Prospective studies have shown no increase in disease-free survival with increased efforts at local control.[30,31] An explanation for the contradictory evidence may be that local recurrence is poorly defined and is actually a manifestation of 2 different problems—microscopic remnants of less aggressive tumor versus a more biologically advanced cancer. Evans[5] coined the term local persistence to describe a local recurrence of a tumor secondary to an imperfect surgical resection leaving tumor cells in the perisurgical bed. Local persistence of disease does not take into account the biological aggressiveness or the host's immunologic suppression of the tumor, therefore, its impact on survival is less predictable. The idea of local persistence of a less biologically aggressive lesion may explain why our patient's tumor recurred locally so late and yet never progressed to systemic disease. His tumor grade, immunologic reaction, and other host biological and environmental factors are unaccounted for but may have played a role in suppression over so many years.

Our patient had a local recurrence but continued to show no evidence of systemic disease, despite not receiving adjuvant radiation therapy (RT) or chemotherapy. Were local recurrence alone used as a measure of potential metastasis and disease-related mortality, adjuvant RT would have been deemed necessary during management of the recurrent lesion. It is well known that adjuvant RT reduces the incidence of recurrent disease in the extremities.[4,31] However, this patient's initial tumor was managed successfully with surgical resection alone, and there was no evidence of recurrence for more than 20 years. The patient experienced minimal morbidity and maintained excellent function of the elbow without the negative effects (eg, elbow stiffness, nerve dysfunction, wound complications) associated with RT.[32] Factors considered during management of this recurrent lesion included its small size (<5 cm) and superficial location. The time between initial presentation and recurrence was also considered a positive prognostic sign, indicating a less aggressive biological pathology.[33-35] Consideration of the biological nature of local recurrence provides a more accurate understanding of the implications of local recurrence for disease-related mortality.[34] Choong and colleagues[33] formulated the growth rate index, a grading system that correlates prognosis with biological characteristics of the tumor—such as size, histologic grade, time to local recurrence, and degree of necrosis. A similar staging system was devised by Ramanathan and colleagues,[35] who took into account size, grade, and time to recurrence. Each of these factors was scored 1 to 3, and a cumulative index representing risk stratification groups was developed. Low-, intermediate-, and high-risk groups correlated with 5-year disease-free survival rates of more than 90%, 50%, and less than 20%, respectively. Patients with concomitant local recurrence and metastatic disease had the worse survival rate (median survival, ~12 months). In our patient's case, the time to local recurrence, the small size of the lesion, and the superficial location of the lesion (easy to monitor) affected our decision to manage the recurrence with surgical excision alone.

Current STS surveillance guidelines recommend monitoring for recurrence annually or semiannually for up to 10 years.[36] MRI of the primary site and CT of the lungs are effective in evaluating for local recurrence and pulmonary metastasis, respectively. Observation over 10 years allows for effective detection of the vast majority of cases of STS recurrence.[36] In our patient's case, the tumor recurred long after the recommended observation period. This is a rare phenomenon and likely the most remote documented recurrence of an extremity STS. We do not recommend changing monitoring guidelines on the basis of the present report alone, but the potential for late recurrence of STS exists and should be considered during long-term management.

Summary

In this report, we have presented the case of a myxofibrosarcoma that recurred 2 decades after surgical excision. Over the same period, STS nomenclature and identification methods have changed substantially. Genetic and immunohistochemical identification methods were unavailable 20 years ago, so we used histologic comparisons to identify our patient's recurrence. What may account for the long time between initial presentation and recurrent disease is a complex phenomenon involving surgical, biological, and host immunologic factors. Features that indicate the biological nature of recurrent lesions—such as time to local recurrence—are important in management planning and prognosis. In most cases, monitoring for recurrence annually or semiannually over 10 years is effective. Nevertheless, the potential for remote recurrence should be considered.

Authors' Disclosure Statement

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This paper will be judged for the Resident Writer's Award.