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Original contribution

Ossifying fibromyxoid tumor: a study of 6 cases of atypical and malignant variants☆

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Summary Ossifying fibromyxoid tumors (OFMT) of soft parts are rare, slow-growing tumors that have potential for local recurrence and may metastasize. While OFMT originally was considered benign, several cases of malignant OFMT have been documented. There is no universally accepted risk stratification, although this study emphasizes the importance of utilizing histology, immunohistochemistry and FISH in establishing the diagnosis. Herein, we describe six cases of atypical and malignant OFMT with differences in morphologic features, 5 of which display the proposed morphological criteria for malignancy. The patients were mostly male (M = 5, F = 1) with an age range of 33–69 years. The tumors arose from the extremities (3 cases), the shoulder (1 case), the head and neck area (1 case), and the paraspinal area (1 case). One tumor had high grade and overtly sarcomatous changes, while another invaded the underlying clavicle. Two cases showed cytological atypia and necrosis. Fluorescence in situ hybridization (FISH) detected rearrangement of the *PHF1* gene in 5 cases. All cases were positive for EAAT4 and actin by immunohistochemistry, while negative for desmin. Three tumors were immunoreactive for S100 protein. INI-1 immunohistochemical staining was conserved in all but 2 cases in which a mosaic loss of expression was noted. All but two patients are currently alive and free of disease.

1. Introduction

Ossifying fibromyxoid tumor (OFMT) of soft parts was first described by Enzinger in 1989 [1]. These tumors occur mostly in the extremities, trunk, and head and neck in decreasing frequency [1]. Macroscopically, they are usually small, circumscribed, and vaguely lobular with a peripheral shell of bone in the majority of cases [2]. Microscopically, the neoplasms are composed of anastomosing cords and sheets of bland, round cells embedded in a fibromyxoid, chondroid, or hyalinized matrix with a peripheral shell of bone [2]. Immunohistochemical stains reveal tumor cells positive for S100 protein and desmin [3]. GFAP, keratins, and smooth muscle actin also may be variably expressed [2,3]. In a small number of cases, the *INI1* gene is deleted corresponding to the loss of nuclear expression of INI-1 by immunohistochemistry [3]. FISH studies have demonstrated a recurrent *PHF1* gene rearrangement in 49% to 79% of typical, atypical, and malignant cases of OFMT [3-9]. The *PHF1* gene is mapped to the short

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arm of chromosome 6 (6p21). Classical cytogenetic studies of OFMT demonstrated clonal abnormalities including loss of chromosome 6 and an unbalanced translocation involving the short arm of chromosome 6 and the long arm of chromosome 14 among other chromosomal aberrations [4-6]. Although originally OFMT was considered benign [1], there have been several reported cases of malignant OFMT [3,10-15]. Features associated with recurrence or metastatic potential include high cellularity, high nuclear grade, and a mitotic count greater than 2 mitoses per 50 high-power fields [14]. The proposed risk stratification has not been universally accepted [2,14]. Herein, we describe 6 cases of atypical and malignant OFMT with differences in morphologic features, 5 of which display the proposed morphological criteria for malignancy.

2. Materials and methods

Following approval by the University of Pittsburgh institutional review board, OFMT from six patients were identified from the archived files of the Department of Pathology of the University of Pittsburgh Medical Center. Hematoxylin and eosin–stained slides were reviewed. Each case had histologic features of typical OFMT. Clinical details and follow-up information were available in all cases. Radiological information was obtained when available. At the initial diagnosis, individual tumors had been subjected to a standard panel of immunohistochemical stains that included CD34 and various epithelial, muscle, and melanocytic markers. In two cases, fluorescence in situ hybridization (FISH) studies had been performed to exclude synovial sarcoma and Ewing sarcoma.

For this study, additional immunohistochemical stains for EAAT4 (Excitatory amino acid transporter-4), INI-1, and CD56 were performed on all 6 cases. Negative and positive controls were appropriate. FISH for *PHF1* was performed on 4-μm-thick sections of formalin-fixed paraffin-embedded tissue blocks. Hematoxylin and eosin sections were used to determine the areas of the tissue to be targeted for analysis. Slides were deparaffinized in xylene twice for 10 minutes, dehydrated twice with 100% ethanol and then pretreated using the Vysis Paraffin Pretreatment Kit (Abbott Molecular, Des Plaines, IL). Slides were digested in protease solution (0.5 mg/ml) at 37°C. *PHF1* FISH was performed using a dual-color break-apart probe labeled in Spectrum Green and Spectrum Orange (Empire Genomics, Buffalo, NY). The target slide was denatured in 70% Formamide at 75°C for 5 minutes and dehydrated in 70%, 85%, and 100% ethanol. Slides were incubated with probe overnight at 42°C in a humidified chamber. Post-hybridization washes were performed using 2XSSC/0.3% Igepal at 73°C for 2 minutes (Sigma, St. Louis, MO). Slides were air-dried in the dark and counterstained with DAPI/antifade (Abbott Molecular). Only individual and well-delineated cells were scored. Overlapping and truncated cells were excluded from the analysis. Approximately 60 tumor cells were analyzed in the targeted region.

3. Results

Clinicopathologic data and ancillary tests results are summarized in Tables 1 and 2.

3.1. Case 1

This 58-year-old man presented with a liver nodule diagnosed as sarcoma on a fine needle aspirate in April 2003 and underwent resection of bilateral paraspinal masses, 2.1 cm (right) and 11.5 cm (left) in August 2003. Histologic sections showed well-circumscribed, lobulated tumors, each with a fibrous capsule and incomplete rim of bone. The neoplasms had characteristic features of OFMT: small ovoid cells with indistinct cytoplasmic borders arranged in nests and cords in a richly vascularized, variably hyalinized fibrous to myxoid stroma. Areas of necrosis and mitotic figures in the range of 3 mitoses per 20 high-power fields were noted. The patient had a medical history of a right calf lesion diagnosed in 1982 as sarcoma; however, the histologic slides were not available for review. Immunohistochemical stains revealed strong nuclear positivity for S100 protein and weak positivity for smooth muscle actin. The liver lesion had a similar immunophenotypic profile. The patient was lost to follow up and died 50 months after diagnosis. The cause of death is unknown.

3.2. Case 2

This 67-year-old woman had a 1.8 cm mass resected from the right upper arm in December 2006.

Histologic examination revealed the characteristic features of OFMT with an infiltrative growth pattern. There were 3 mitoses per 10 high-power fields and no microscopic necrosis. The patient was free of disease in March 2009.

3.3. Case 3

This 69-year-old man underwent partial excision of a 3.5 cm lump on his foot initially interpreted as high-grade fibromyxoid sarcoma in 2007. Because of extensive metatarsal involvement, he elected to have a below knee amputation in November 2007. Chest x-ray a year later revealed lung nodules within his right upper lobe suspicious for metastatic disease. The patient died 36 months later with metastatic tumor. Histological examination of the amputated leg tumor revealed characteristic features of OFMT with prominent myxoid areas and cellular regions composed of sheets of round cells reminiscent of Ewing sarcoma (Fig. 1). There were 5 mitoses per 10 high-power fields, and foci of microscopic necrosis. Initial FISH studies did not reveal rearrangements for *EWSR1* and *SS18* (*SYT*). FISH revealed rearrangement of *PHF1* (Fig. 2).

3.4. Case 4

A 3.0 cm parotid mass was resected from a 33-year-old man in 2012. Histologic sections showed a well-circumscribed,