Reduced S100 Protein Expression in Malignant Ossifying Fibromyxoid Tumors: A Case Report

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Summary: Ossifying fibromyxoid tumor of soft parts (OFMT) is a rare mesenchymal neoplasm of uncertain lineage. OFMT normally has a benign clinical course, and malignant variants are considered unusual. Criteria defining malignancy have not yet been clearly identified and universally accepted, and there is diagnostic uncertainty between pathologists as to how best to recognize a malignant variant. We present the case of a 68-year-old male patient who, following initial diagnosis of typical OFMT in the left scapular region, presented to the sarcoma service 9 years later with a short history of a solid lesion in the right calf. Biopsy confirmed metastatic OFMT and further imaging identified three other radiologically similar but distant lesions, which were later resected. The histology of the initial biopsy was reviewed, and the original observations were found to be accurate and due to current diagnostic criteria, the specimen was reported as typical. We propose that this case report contributes to a growing body of literature suggesting that negative S100 expression may be a useful feature in identifying and characterizing malignant OFMT. (Plast Reconstr Surg Glob Open 2021;9:e3482; doi: 10.1097/GOX.0000000000003482; Published online 23 March 2021.)

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First described by Enzinger et al in 1989, an ossifying fibromyxoid tumor (OFMT) is a rare soft tissue and bony neoplasm considered to be mesenchymal in origin. OFMT almost exclusively occurs in adults, with a median age of approximately 50 years. These painless tumors usually present as well-circumscribed, firm nodules in skeletal muscle or subcutaneous soft tissue, with a predilection for the extremities.

In its classical form, the macroscopic appearance of OFMT is characterized by a lobular architecture that is grey-white in color. Microscopically, the tumor is composed of uniform epithelioid cells with very low mitotic activity, arranged in nests within a variably myxoid stroma.

In 2003, Folpe and Weiss conducted a large retrospective analysis of 70 cases of OFMT. Over a median follow-up of 36 months, the association between the tumor’s microscopic features and rates of local recurrence or distant metastasis was studied to develop a risk-stratified classification system. “Typical” tumors, with a low nuclear grade, low cellularity, and low mitotic rate, resulted in a 4% rate of metastasis. The “malignant” subgroup, characterized by the presence of high nuclear grade or a high cellularity and mitotic activity, was predictive for local recurrence in 60% of cases and metastasis in 60% of cases. The “atypical” subgroup of intermediate risk had features distinct from typical OFMTs, but not meeting the recommended criteria for the malignant subgroup. The current standard of care for “typical” variants involves localized resection, without chemotherapy or radiotherapy.

Nevertheless, the Folpe and Weiss classification is not universally accepted and, due to the unusual behavior of the tumor, there is still confusion and uncertainty between pathologists about how to recognize a malignant variant of OFMT.

CASE PRESENTATION

A 68-year-old White man was referred to the sarcoma service in June 2015, with a 6-month history of a solitary, painless, enlarging lump in his right calf. His first and only symptom was calf tightness noticed while jogging. There was no history of weight loss, night sweats, nor dyspnea to suggest metastases. He denied trauma, and there was no relevant family history. He had been an ex-smoker for the last 40 years. Past medical history included hypertension and a typical OFMT in the left subscapular region,
which was completely excised in 2006, under the care of the General Surgery Department.

On examination, there was a 25 × 55 mm non-tender, smooth, hard, oval mass in the right calf. The overlying skin was tethered to the tumor and fixed on calf contraction. There was no palpable inguinal lymphadenopathy. A plain film identified a calcified lesion that, in the context of the previous diagnosis, was suspicious of OFMT (Fig. 1). A core biopsy from the right calf reported a monomorphic proliferation of ovoid cells in a myxoid matrix, with rare mitosis, and no necrosis; the immunohistochemical (IHC) profile was negative for S100. Overall, the appearances were suspicious but not conclusive of OFMT.

The patient underwent excision of the right calf lesion by a sarcoma surgeon under general anesthetic in August 2015. The medial gastrocnemius was excised with a strip of soleus fascia and muscle (Fig. 2). The overall morphology and IHC profile favored OFMT and in view of the clinical history, the lesion was regarded as a metastasis. The patient recovered well from surgery and was discharged 5 days later. The patient did not have chemotherapy or radiotherapy.

Given the apparent metastatic nature of the disease, the original histology report of the primary left subscapular tumor excision biopsy (2006) was reviewed and demonstrated hypercellular stroma with high mitotic activity but no atypia or significant hypercellularity; there was negative S100 expression (Fig. 3). The initial observations were found to be accurate, confirming typical OFMT, although the criteria for malignancy remain controversial.

**Outcome and Follow-up**

Computerized Tomography (CT), magnetic resonance imaging, and CT with positron emission tomography (CT-PET) identified three other distant and radiologically similar lesions—one at the left costo-chondral junction of the second rib; one in the right para-spinal muscles adjacent to T7; and one in the left para-vertebral muscles adjacent to the spinous process of L1 (Fig. 4). These metastatic lesions were excised with clear margins. Typical OFMT metastases usually have an indolent course and so the patient was monitored with ongoing CT-PET scans at 6 months, and annually thereafter. A further histologically similar lesion in the right gluteus maximus was identified and successfully excised in June 2018. Follow-up is ongoing at the time of writing in November 2020.

**DISCUSSION**

In this case, histology of the primary tumor revealed minimal nuclear atypia and no mitotic nor apoptotic cells, thereby excluding the diagnosis of “malignant” OFMT according to the Folpe and Weiss criteria. However, it has been suggested that the absence of S100 protein, as exemplified in this case, may indicate malignant behavior.

Typical OFMT tumors demonstrate immunoreactivity for vimentin (100%), S100 (94%), CD10 (79%), pancytokeratin (13%), and collagen IV (13%).

Diffuse S100 expression is a useful immunohistochemical marker in reinforcing a diagnosis of OFMT, but is not necessary for such a diagnosis.

The absence of S100 expression in the presence of other cytoarchitectural and immunohistochemical indicators of OFMT may be related to malignant transformation. Folpe and Weiss (2003) did not find a strong
relationship between S100 expression and overall tumor appearance, with expression in 72% of typical and 50% of atypical tumors. However, the relationships between S100 expression and malignant OFMT, and clinical outcomes, were not stated. In one case series, expression of S100 protein varied significantly across subcategories: 88% of typical, 75% of atypical, and 42% of malignant OFMT. In a more recent case series, Antonescu et al observed that most malignant OFMTs were negative for S100, with only 27% of malignant cases demonstrating expression, which was only ever focal, and never diffuse. In contrast, 88% of typical and atypical tumors demonstrated S100 expression.

CONCLUSIONS
We believe the findings of this case support the already existing literature suggesting that negative S100 expression, especially diffuse, may be a useful indicator of malignant OFMT. Further large-scale studies are required to definitively establish this relationship.

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