Ossifying Fibromyxoid Tumor

An Update

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• **Ossifying fibromyxoid tumor (OFMT) is a rare soft tissue neoplasm of uncertain differentiation, initially described by Enzinger and colleagues. Until now, nearly 300 such cases have been reported worldwide. The histogenesis of these tumors remains controversial. These tumors show characteristic imaging findings and exhibit a spectrum of histopathologic features, including classical and atypical subtypes. Local recurrences and, occasionally, distant metastases have also been reported. A complete tumor resection forms the preferred treatment modality for these tumors, along with follow-up, as these tumors have an uncertain malignant potential. Lately, certain "molecular signatures" underlying OFMTs have been described that can further aid in reaching an accurate diagnosis for these tumors and unraveling their pathogenesis. This article is a review of the clinical, radiologic, histopathologic, and molecular features of OFMTs.**

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Ossifying fibromyxoid tumor (OFMT) is a rare musculoskeletal tumor of borderline malignant potential, displaying an uncertain line of differentiation.[1] Enzinger et al[2] reported this unique soft tissue neoplasm, which presented as a well-circumscribed nodular mass in the subcutaneous tissues or muscles, and designated it as an OFMT of soft parts. Since then, several case reports and series of OFMTs have been documented, the latter by Folpe et al[3] and Miettinen et al.[4] Ossifying fibromyxoid tumor is now a well-recognized tumor entity, with recent studies unearthing specific gene fusions and translocations in these tumors.[5,6] Atypical and malignant OFMTs have been described on the basis of certain histopathologic parameters.[3,4,7] However, there are different views regarding correlation of the malignant subtype with metastatic potential.[1,3] Nonetheless, an accurate diagnosis of an OFMT is essential to distinguish this tumor from its differential diagnoses.

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CLINICAL FEATURES

Ossifying fibromyxoid tumors occur in adults of all ages, mostly in middle-aged individuals, and are slightly more common in men within an age range of 14 to 83 years, with median age approximately 50 years.[1–4] These tumors mostly occur in the subcutaneous soft tissues or skeletal muscles of the extremities (proximal more common than distal). These tumors have also been reported at other sites, such as trunk, head and neck, oral cavity, mediastinum, spine retroperitoneum, and breast.[1,2,7–10] They present as small, well-circumscribed, painless, deep-seated tumor nodules often attached to the underlying tendons, fascia, or skeletal muscles. These tumors usually have a longstanding clinical course, ranging from 1 to 20 years or even of longer duration (median, 4 years).[11] Their size ranges from 1 to 14 cm (average, 4–5 cm).[3,4]

RADIOLOGIC FINDINGS

On radiographic examination, an OFMT presents as a nodular soft tissue mass with an incomplete peripheral rim of ossification.[12] The underlying bone may be eroded or may show features of periosteal reaction.[2] Computed tomography (CT) scan usually reveals a peripheral "bone shell" in at least 60% to 70% of cases.[2,3] Technetium scans also reveal presence of intratumoral mature bone formation in the form of increased uptake.[13] Magnetic resonance imaging (MRI) findings are quite variable. This tumor is isointense to muscles on T1-weighted images and shows intermediate to high signal intensity on T2-weighted images. There are high signal intensity areas on T1- and T2-weighted images, suggesting hemorrhage and implying a high degree of vascularity. In addition, areas of ossification demonstrate low signal intensity on T1- and T2-weighted images.[12] On radiologic examination, the differential diagnoses include, among others, an ossifying hematoma and myositis ossificans.[13] Radiologic findings are helpful with small biopsy specimens. In most cases with tumor size up to 2 cm, a complete tumor resection is performed and the specimen is submitted for histopathologic examination.

PATHOLOGIC FEATURES

Grossly, these tumors are encapsulated with a surrounding fibrous or fibro-osseous pseudocapsule seen in most cases.[1–4] An incomplete peripheral layer of lamellar bone may or may not be seen. Cut surface of the tumor is generally lobulated, firm to rubbery, and has a myxoid appearance (Figure 1).

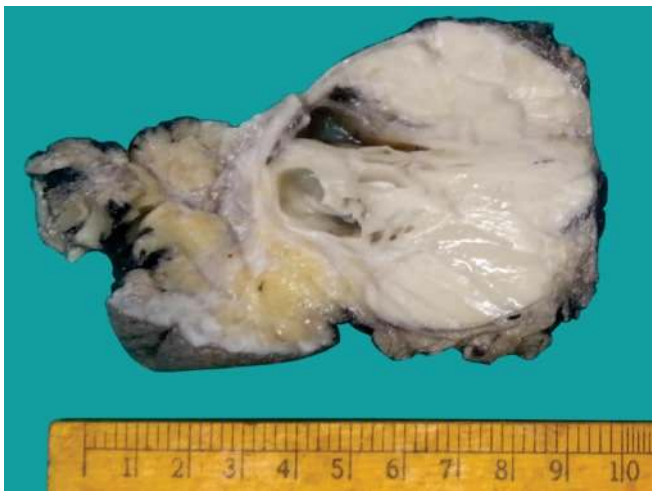

Figure 1. *Gross findings of an ossifying fibromyxoid tumor. Subcutaneous, well-circumscribed multinodular tumor with grey-white glistening cut surface, exhibiting multiple cysts.*

Microscopically, the tumor is composed of lobules of small, polygonal to spindle-shaped cells with vesicular nuclei, discernable nucleoli, and eosinophilic cytoplasm, arranged in cords, trabeculae, or in clusters in a loose fibromyxoid matrix (Figure 2, A and B).[1–4] The tumor cells are uniform and bland with cell-to-cell spacing.[2] A few lesions may show small "tongues" of infiltrating tumor cell nests.[3] Mitotic figures may be seen, whereas necrosis and vascular invasion are uncommon. Variable histopathologic features include presence of metaplastic bone formation, mucinous microcysts, and chondroid differentiation.[1,3,4] Further, 3 microscopic subtypes of OFMTs have been previously described, namely, typical, atypical, and malignant, based on cellularity, nuclear grade, and mitotic activity. In one of the premier studies, Folpe et al[3] described tumors characterized by high grade or high cellularity and mitotic rate greater than 2 mitoses per 50 high-power fields (HPFs) as malignant OFMTs, as such cases were found to be associated with distant metastasis. Tumors deviating from the features of a typical OFMT, but not meeting the criteria for malignancy, were categorized as atypical subtypes (Figure 3, A and B).[3] Subsequently, in an elegant study, Miettinen et al[4] reported no tumors with higher mitotic

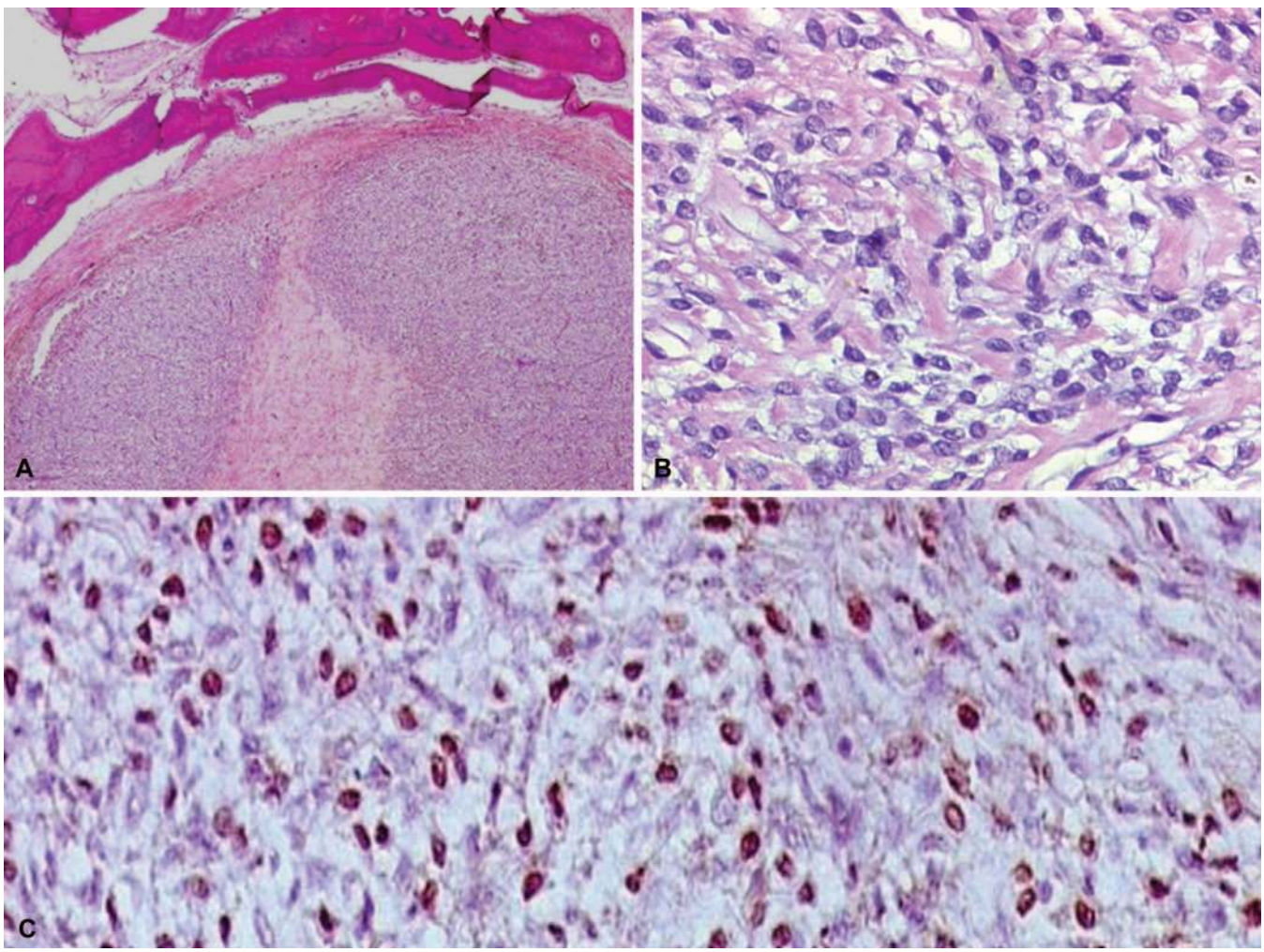

Figure 2. *Microscopic findings. Typical ossifying fibromyxoid tumor (OFMT). A, Multinodular, well-circumscribed tumor with a peripheral shell of lamellar bone. B, Higher magnification showing cellular tumor composed of rather banal, polygonal to short spindly cells with eosinophilic cytoplasm, arranged in cords in a fibromyxoid stroma. C, Tumor cells displaying diffuse S100 expression (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]; diaminobenzidine, original magnification ×400 [C]).*

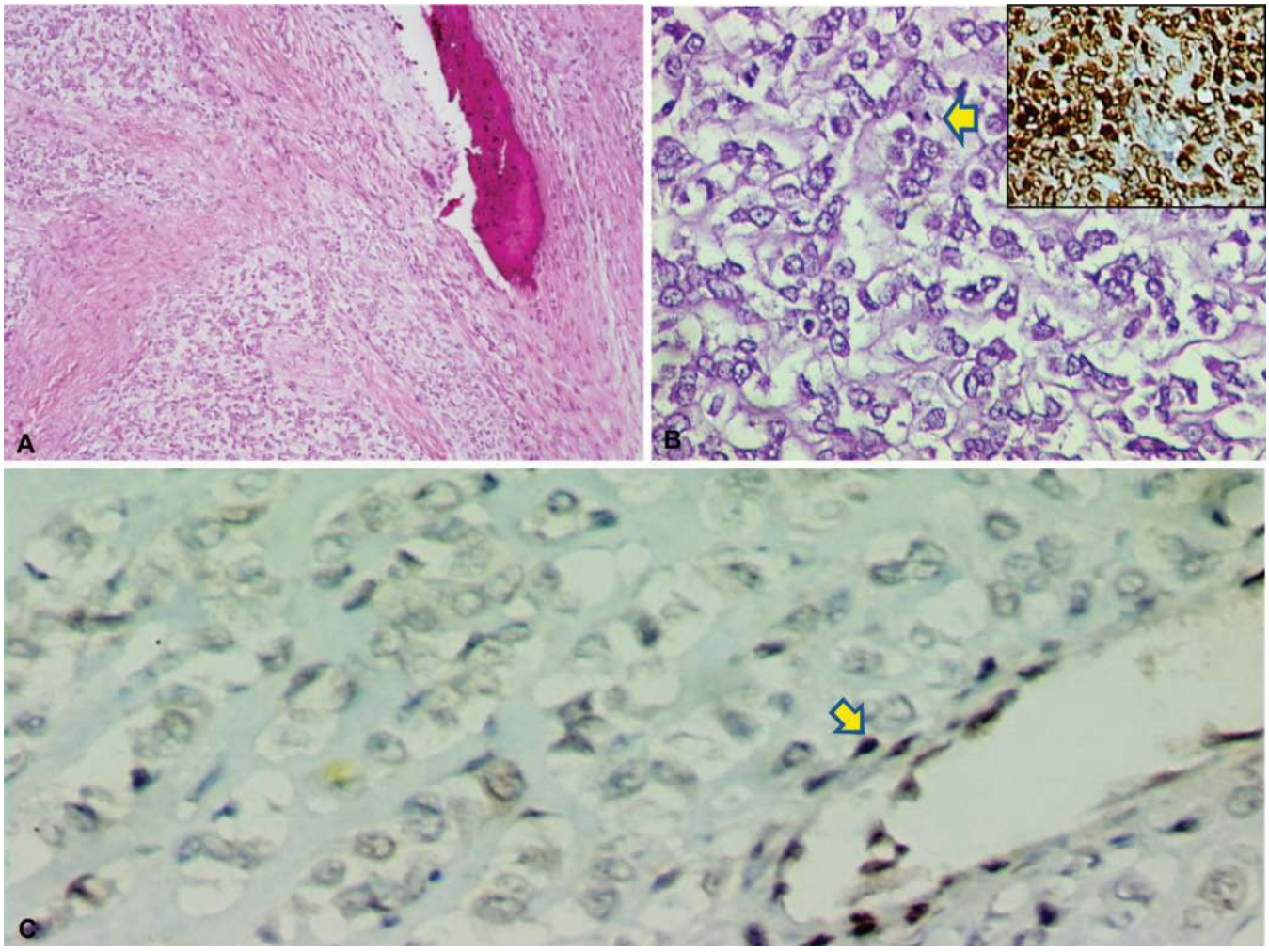

Figure 3. *Microscopic findings. Atypical ossifying fibromyxoid tumor. A, Multinodular tumor with fragment of lamellar bone. B, Higher magnification displaying tumor areas with increased cellularity, higher atypia, and mitotic figures (arrow). Inset: Tumor cells displaying diffuse S100 expression in certain areas. C, "Mosaic" pattern of weak to absent INI1/SMARCB1 expression. Endothelial cells (arrow) acting as internal positive control (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]; diaminobenzidine, original magnification ×400 [inset B and C]).*

counts that were metastasizing. They observed that tumors with mitotic counts greater than 2 per 50 HPFs were associated with local recurrences. Perhaps such cases can be designated as "atypical" variants.[1] Graham et al[7] described tumors with areas of nuclear crowding and loss of intervening matrix, occupying at least 1 low-power field, as "highly cellular." Some OFMTs exhibiting typical features along with focal malignant areas have been designated malignant OFMTs.[3] Cases of malignant OFMTs arising in a background of typical OFMT, as well as such tumors showing benign and juxtaposed malignant areas, have also been described. While one of these reported cases showed recurrence, the other 2 cases lacked follow-up.[8,14] Therefore, existence of fully malignant OFMTs is still a subject of discussion.

Immunohistochemically, OFMTs display S100 protein expression, more in the typical than in the malignant subtypes, as observed in all major studies[3,4,15,16] (Figure 2, C). Antonescu et al[16] observed S100 expression in 60% of cases of OFMT. They observed that most malignant OFMTs were negative for S100, with only 4 cases showing focal or more diffuse staining. Certain tumors have also revealed coexpression of desmin, vimentin, epithelial membrane antigen, and smooth muscle actin, EAAT4, MUC4, NFP, and CD56.[7,16] CD10 positivity has also been documented in a case of OFMT with atypical histologic features.[1,13] Recently, Graham et al[7] have described a characteristic "mosaic" pattern of loss of INI1/SMARCB1, unlike other authors[14] who observed retained INI1 expression in 2 malignant OFMTs (Figure 3, C).

DIFFERENTIAL DIAGNOSES

Histopathologically, the differential diagnoses include sclerosing epithelioid fibrosarcoma, calcifying fibrous pseudotumor of digits, malignant peripheral nerve sheath tumor, synovial sarcoma, ossifying hematoma, and an ossifying epithelioid hemangioendothelioma.[14] Lack of epithelial markers and conspicuous S100 expression with aforementioned histopathologic features are helpful in differentiating an OFMT from a sclerosing epithelioid fibrosarcoma and a synovial sarcoma; the latter displays focal, rather than diffuse, S100 expression. Epithelioid hemangioendothelioma displays immunohistochemical positive expression with vascular markers such as CD34, CD31, and Fli1. In view of

Review of Genetic Abnormalities Underlying Ossifying Fibromyxoid Tumors				
Serial No.	Source, y	No. of Cases	Cytogenetic Findings, Gene Rearrangement	Chromosomal Translocations, Gene Fusion(s)
1	Sovani et al,[23] 2001	1	Loss of chromosome 6, extra material of unknown origin attached to the long arm of chromosome 12	45, XY, der(6;14)(p10;q10), add(12)(q24.3)
2	Gebre-Medhim et al,[6] 2012	16	*PHF1* rearrangement in 10 of 16 cases (62.5%)	t(6;12)(p21;q24.3) *EP400-PHF1* fusion in 1 of 3 cases
3	Graham et al,[5] 2013	41	*PHF1* rearrangement in 20 of 41 cases (49%)	. . .
4	Endo et al,[26] 2013	1	*PHF1* rearrangement; single case	t(6;12)(p21;q24.3) *EP400-PHF1*
5	Antonescu et al,[16] 2014	39	*PHF1* rearrangement in 31 of 39 cases (79%), *BCOR* rearrangement in 1 case	t(6;12)(p21;q24.3) *EP400-PHF1* fusion in 40% of cases; *ZC3H7B-BCOR* in 1 case and *MEAF6-PHF1* fusions in 3 tumors that were S100 negative and were malignant subtypes; *EPC1-PHF1* fusion in 2 additional cases

S100 positivity, a schwannoma can be a rare differential diagnosis, on limited biopsy.[17]

The etiopathogenesis and exact line of differentiation of an OFMT is presently unclear. Evidence exists for a schwannian or neuronal differentiation but this has not been well proven.[18–20] Similarly, cartilaginous or myoepithelial differentiation was proposed by Enzinger et al[2] and Kilpatrick et al,[15] respectively. From these hypotheses, Graham et al[7] suggested a "scrambled" phenotype for these tumors.

On ultrastructural examination, the cytoplasm may contain dense-core granules measuring 100 to 200 nm and abundant filaments of an intermediate size. These dense-core granules with antidesmin positivity seem to indicate possible myoepithelial or partial smooth muscle differentiation. A few filopodia-like processes, discontinuous basal lamina, and a few primitive cell junctions may exist ultrastructurally.[2,15] These findings were found to be suggestive for neural or smooth muscle origin of the neoplasm. Hanski and Lewicki[21] identified 2 cases of OFMT histologically and ultrastructurally, revealing multinucleated, vimentin and S-100 protein–positive "fibroblastoid" cells. They proposed that these tumors are mesenchymal multipotential derivatives of fibroblastoid origins. Later, Min et al[22] observed that tumor cells in OFMT were mostly polygonal to stellate, with multiple short cytoplasmic processes, forming cell clusters attached by primitive intercellular junctions between cytoplasmic processes forming intercellular bridges. They noted that cell borders facing the stroma around cell clusters tended to be flat and had incomplete external lamina, while no external lamina was present along the cell borders facing the inner aspect of cell clusters. They postulated that these ultrastructural findings, together with immunophenotypic expression of S100 protein, were indicative of modified myoepithelial cells as the possible cell of origin of OFMTs.

MOLECULAR/GENETIC FEATURES

Initially, Sovani et al[23] identified clonal chromosomal abnormalities including loss of a chromosome 6; extra material of unknown origin attached to the long arm of chromosome 12; and an unbalanced translocation involving the short arm of a chromosome 6 and the long arm of a chromosome 14 in a case of OFMT. Subsequently, Nishio et al[24] and Kawashima et al[25] identified numeric and structural aberrations, respectively, in a single OFMT each. Recent studies have unraveled specific molecular translocations underlying OFMTs. A novel fusion gene, namely, *EP400-PHF1*, located on chromosome band 6p21, has been identified in OFMTs along with compatible cytogenetic data showing a t(6;12)(p21;q24.3) translocation.[5,16] *PHF1* gene rearrangement has been observed in 80% of OFMTs, including benign, atypical, and malignant subtypes, with fusion to *EP400* in 44% of cases.[26] The PHF1 protein interacts with the polycomb repressive complex 2 (PRC2), which in turn, regulates the expression of a variety of developmental genes. *PHF1* encodes the PHD finger protein 1 (PHF1), which is involved in chromatin structure regulation, forming polycomb repressive complex 2 (PRC2) with EZH1, EZH2, SUZ12, regulating histone H3 lysine 27 (H3K27) methylation. *ZC3H7B-BCOR* and *MEAF6-PHF1* fusions have been identified predominantly in S100-negative and malignant OFMTs.[16] These findings suggest that OFMTs may represent translocation-associated sarcomas.[3] *PHF1* gene rearrangements have also been described in endometrial stromal sarcomas (ESSs), suggesting a similar role in their pathogenesis (Table).[6,16,26]

Graham et al[7] documented deletions of the *SMARCB1/INI1* gene, located on 22q11.2, in 71% of cases, as detected by fluorescence in situ hybridization. Anomalies have also been reported in chromosomes 6, 12, and 14. Gene expression profiling has revealed clustering of typical and malignant OFMTs together, distinct from schwannian tumors. In addition, down-regulation of genes expressed in schwannian cells, such as peripheral myelin protein 22 (PMP22) and myelin expression factor 2 (MYEF2), has been observed. DNA microarray study has unraveled a neuron-associated gene, *EAAT 4*, expressed at high levels in OFMTs.

Proteomic studies have revealed overexpression of collagens 1A1, 1A2, 6A3, and type 2 in a few OFMTs. In addition to abundant katanin (a neuron-associated microtubule-severing protein), versican (a neuron-associated proteoglycan) has also been identified in verified cases of OFMT.[7]

MANAGEMENT AND FOLLOW-UP

Surgical excision is the treatment of choice, along with a close follow-up, especially in atypical and malignant types, because of this tumor's propensity for local recurrences and distant metastases. Metastases have been reported only in the malignant type of OFMT, while death due to disease

was observed in 10% of patients who had metastatic disease.[3]

CONCLUSIONS

Ossifying fibromyxoid tumor represents a distinct soft tissue tumor with characteristic histopathologic features, including its typical and atypical subtypes. S100 expression is the most consistent immunohistochemical marker for reinforcing diagnosis of OFMT in most cases. However, these tumors lack unequivocal nerve sheath origin. *PHF1* gene rearrangement seems to be the most significant underlying genetic event within OFMTs, leading to their inclusion in the group of translocation-related sarcomas. Recent studies have shown similar rearrangement in ESSs, indicating genetic proximity between ESSs and OFMTs in certain cases, despite unequivocal clinicopathologic differences between these 2 tumors. Certain OFMTs display a characteristic "mosaic" pattern of loss of INI1/SMARCB1.

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