Ossifying fibromyxoid tumor (OFMT) is a rare mesenchymal neoplasm of uncertain histogenesis demonstrating intermediate malignant potential, and it was first described by Enzinger and colleagues. They reported a series of well-circumscribed masses arising in the subcutis or deep soft tissues, characterized by a proliferation of small epithelioid cells with round, vesicular nuclei, arranged in cords or nests in a myxoid and hyaline stroma. A high proportion of these cases showed immunoreactivity for S100 protein, as well as an incomplete shell of lamellar bone based in the fibrous capsule. The authors suggested the possibility of cartilaginous or neural origin, given the combination of S100 protein expression and matrix characteristics. Despite other studies showing desmin expression in a subset of tumors, indicating a potential for myoid or myoepithelial differentiation, as well as additional ultrastructural descriptions postulating a similar cell of origin, the relatively low rate and often focal expression pattern of myoid markers argued against this supposition.

Early cytogenetic studies demonstrated losses or unbalanced translocations involving chromosome 6, and this finding, in combination with the morphology of an often cytologically uniform tumor with histologic stability between initial tumors and metastases, led to the prediction that OFMT was a translocation-associated tumor. Subsequent descriptions also lead to the elucidation of histologic features associated with adverse outcomes, with such cases being labeled as “malignant” OFMT.

**MOLECULAR GENETICS**

Initial insights provided the foundation for more recent discoveries on the genetic drivers of OFMT. The most common genetic rearrangements found in OFMT is that of the *PHF1* gene on 6p21. This alteration is found in between 50% and 85% of cases in the largest available case series. *PHF1* encodes a protein that controls expression of genes in embryonic stem cells related to differentiation in fetal development through a complex interaction with the product of the polycomb-repressive complex 2 gene (*PCG2*), resulting in changes to chromatin structure through additional interactions with EZH1/2 and SUZ12, leading to regulation of histone H3 at its lysine 27 methylation (H3K27 methylation) site. The most common fusion partner is *EP400* on 12q24.3, present in approximately one-half of cases and most commonly due to a single balanced translocation. Other fusion partners...
include MEAF6 and EPC1, the resulting fusion products of which have also been described in endometrial stromal sarcomas.\textsuperscript{9} A number of cases with PHF1 rearrangements with unknown fusion partners have also been described. RNA sequencing (RNA-Seq) was instrumental in the subsequent description of 5 cases of OFMT harboring a recurrent PHF1-TFE3 fusion, and this technique will be useful in further expanding the morphologic and genetic spectrum of this entity.\textsuperscript{12} Other less frequently encountered fusions include KDM2A-WWTR1, CREBBP-BCORL1, and ZC3H7B-BCOR, some of which have also been described in a recently proposed category of endometrial stromal sarcoma.\textsuperscript{13} These rarer gene fusions not involving PHF1 have been found to correlate with aggressive behavior, in addition to those involving TFE3.\textsuperscript{12} Of note, the genes CREBBP, BCORL1, and KDM2A are also involved in the modification of histones and therefore chromatin structure regulation, similar to the more commonly altered PHF1 gene.\textsuperscript{13} Thus far, cases described with PHF1-EP400 fusions and unknown fusion partners are more likely to exhibit S100 protein and desmin expression.\textsuperscript{9}

Additional genomic and proteomic analyses have also been described, which helped to confirm earlier descriptions of malignant OFMTs. Among a cohort of 13 typical and malignant OFMTs, gene expression profiles between typical and malignant OFMTs were found to be similar. Both typical and malignant OFMTs showed upregulation of EAT14 and MUC4, whereas they exhibited downregulation of MYE2 and PMP22.\textsuperscript{10} This analysis led to additional descriptions of MUC4 expression by immunohistochemistry (described below), an important factor to consider given the morphologic overlap of OFMT with some cases of low-grade fibromyxoid sarcoma (LGFMS) and sclerosing epithelioid fibrosarcoma (SEF). Proteomic analysis has shown the following classes of proteins to be upregulated in OFMTs: matrix proteins, such as collagen types 1A1, 1A2, and 6A3, members of the S-100 family of proteins, and also katanin, and versican (neuron-associated protein and glycoproteins, respectively).\textsuperscript{10}

**Epidemiology and Clinical Features**

Ossifying fibromyxoid tumor affects young, middle-aged, and older adults, with reported cases observed in patients ranging in age from 10 to 88 years. Most cases occur in the fifth and sixth decades (mean, 51 years).\textsuperscript{5,9,10,14–16} It has a slight predilection for men, with a male to female ratio of 1.5:1. The tumors most commonly arise in the proximal limbs and limb girdles, followed by the distal upper and lower limbs, head and neck, and trunk. They are most often based within the subcutaneous tissues, but can affect deep muscle and bone sites as well. Symptoms typically consist of fullness or palpable nodularity at the tumor site, without associated pain. They can be quite large, with tumors reported to range from 0.5 to 21 cm, but the median size is just less than 4 cm.\textsuperscript{1,5,10,12,15,16}

Radiographically, the tumors typically present as soft tissue masses within the subcutis or deep soft tissues, and close inspection of the tumors on computed tomography scans can show peripheral or central calcifications in nearly 70% of cases, with similar opacities seen on plain film radiographs.\textsuperscript{1,5,17} This shows a high correlation with the percentage of tumors that demonstrate histologic evidence of mature lamellar bone formation. These findings are nonspecific, however, as there is significant overlap with more common reactive, nonneoplastic conditions and benign neoplasms, including chronic organizing hematomas with calcification and myositis ossificans.\textsuperscript{18} Magnetic resonance imaging findings are variable, with low signal intensity in ossified areas and isointensity to muscle tissue on T1-weighted images.\textsuperscript{19,20} This overlap supports tissue biopsy of soft tissue nodules with indication of the above entities in the differential diagnosis, particularly in unresolved or progressively enlarging cases.

**Histopathology**

Histologically, most OFMTs are characterized by a moderately cellular proliferation of uniform, round, or ovoid epithelioid cells with defined cytoplasmic borders, centered within a myxohyaline or fibromyxoid stroma (Figure 1, A). The constituent cells most commonly contain moderately abundant pale eosinophilic cytoplasm, but clear cell change can be a feature. The tumor cells are often arranged in cords, a very useful pattern to recognize among tumors within the morphologic differential diagnosis. Other patterns include nests and loose sheets, as well as trabecular and reticular patterns, and the tumor cells are often unevenly distributed throughout the tumor, resulting in variable cellularity from low-power magnification (Figure 1, B). A thick fibrous or hyalinized capsule is a common feature, which may ossify and develop into a thin shell of bone at the periphery of the tumor (Figure 1, C), although this feature should not be overly relied upon because it is absent in almost 30% of cases. Ossification may also be seen in the center of the tumor along interlobular fibrous septa. Importantly, the constituent cells are only rarely seen to be directly producing or embedded within the osteoid, a feature that separates OFMTs with atypia from extraskeletal osteosarcoma.\textsuperscript{13} Despite the low-power perception of circumscription, it is not uncommon for small nests to be present beyond the fibrous capsule, a feature that has not been shown to increase recurrence risk (Figure 1, D).\textsuperscript{13,15} Mitotic activity is typically inconspicuous, usually 2 or fewer per 50 high-power fields. Occasional nuclear atypia can be present, and it is not an adverse prognostic factor in isolation (Figure 1, E).

The proposed features of malignancy associated with more aggressive behavior include either high-grade nuclear features or increased cellularity in combination with a mitotic index greater than 2 per 50 high-power fields. In the study by Folpe and Weiss,\textsuperscript{9} the presence of these features was associated with a recurrence risk of 60% and metastatic risk of 60% (6 of 10 each), compared with recurrence and metastatic rates of typical OFMTs of 8% and 4%, respectively (Figure 1, F).\textsuperscript{2} This dichotomous grading system was supported by 3 additional large cohorts, albeit with lower overall rates of adverse events, which showed a combined rate of recurrence or metastasis in typical OFMT of 0% (0 of 58; median follow-up range, 45–144 months), whereas recurrence and metastatic rates in malignant OFMT were 22% (10 of 32) and 12.5% (4 of 32), respectively.\textsuperscript{10,14,15} Necrosis is not a typical feature even in cases demonstrating malignant behavior, but it can occasionally be present in approximately 13% of cases (22 of 174). Cases of OFMT may have significant heterogeneity within the tumor, with a morphologic spectrum extending from the cytologically bland or typical OFMT to the cytologically malignant, either with gradual or abrupt nodular transitions. However, OFMTs with more uniformly malignant morphologic features are increasing.
ly recognized on the basis of genetics through the use of next-generation sequencing or RNA-Seq, which has allowed for expansion of the morphologic spectrum of this tumor, as well as providing confirmation that malignant cases demonstrate similar overall gene expression profiles.10

Less common morphologic features include pseudoglandular and pericytic growth patterns, rhabdoid morphology, mucinous microcysts, and spindle cell change. One case with pseudoglandular architecture was also shown to exhibit expression of cytokeratins and neuroendocrine differentiation, leading to obvious risk of confusion with a well-differentiated neuroendocrine tumor.12 Extensive cartilaginous metaplasia is seen in rare cases.16 A pericytic growth pattern in which the constituent cells collect around large vascular lumina has also been described.21 Rarely, cases of OFMT with alternate fusions, such as CREBBP-BCORL, can show areas exhibiting striking morphologic overlap with myoepithelial tumors, with small round cells containing bland, uniform nuclei and scant eosinophilic cytoplasm arranged in a reticular pattern within myxoid stroma.19 Ultimately, only about one-quarter of described cases actually fulfill all of the “classic” features, including the typical morphology with peripheral ossification, coexpression of desmin and S100 protein, and the most common fusion EP400-PHF1.

Figure 1. Histologic findings in ossifying fibromyxoid tumor include low-grade epithelioid cells arranged in nests and cords (A), often with variable cellularity and a dense, hyalinized stromal matrix (B), and a collagenous capsule with partial ossification (C). A subset of cases will show small nests beyond the capsule, which does not independently affect prognosis (D). Scattered nuclear atypia can be present, which in isolation is of no prognostic value (E), whereas mitotic activity in excess of 2 per 50 high-power fields significantly increases the risk of local recurrence and metastasis (F) (hematoxylin-eosin, original magnifications ×200 [A], ×100 [B], ×40 [C and D], and ×400 [E and F]).
IMMUNOHISTOCHEMISTRY

The classically described immunophenotype of OFMT includes coexpression of S100 protein and desmin; however, reported rates of desmin expression among large cohorts vary wildly (Figure 2, A and B). Based on the combination of multiple large case series (combined 356 cases), S100 protein is the most reliable immunohistochemical marker, staining an average of 75% of cases (193 of 257), with a higher proportion of typical cases showing positivity (80%), versus lower proportions of atypical and malignant cases (41%).2,5,9,10,14–16 S100 protein positivity can be focal but is more often seen in more than 30% of tumor cells, in both a cytoplasmic and nuclear distribution. Desmin expression is seen in a much lower proportion, with 25% (57 of 172) of cases showing positivity (Figure 2, C). Thus, only about one-quarter of cases exhibit the typical morphologic features in combination with coexpression of S100 protein and desmin.

Other reported markers include rare weak positivity for cytokeratins (18 of 147; 12%), epithelial membrane antigen (EMA; 6 of 87; 7%), and smooth muscle actin (SMA; 7 of 134; 5%). One study observed that cytokeratin expression was only present in the portion of the tumors that were morphologically malignant, and these tumors were also positive for p63.14 Given the high rates of S100 protein expression in combination with epithelioid morphology, it is important to note that no cases with either MART1 or HMB-45 have been reported (0 of 5 and 0 of 17, respectively), although melanocytic tumors or perivascular epithelioid cell tumor family tumors would only be considered in the differential of highly cellular OFMT variants, given the hyaline matrix production of this tumor.14,15 Of comparative greater utility is SOX10, because positivity has only been shown in 4% of cases (2 of 47), which separates OFMTs from epithelioid nerve sheath tumors as well as most myoepithelial tumors (Figure 2, D).22 Similarly, endothelial markers CD31 (0 of 5) and CD34 (0 of 38) are negative in reported cases.14,15 MUC4 can be weakly positive in a significant minority, which differs from the strong, diffuse staining seen in most cases of LGFMS and SEF. This has been shown to be due to an upregulation in MUC4.10

Patchy loss of INI-1 in about 50% of lesional cells has been reported in most tested cases (14 of 19; 74%), but this finding does not correspond with homozygous deletions of SMARCB1, and therefore represents a potential pitfall with epithelioid sarcoma and epithelioid malignant peripheral nerve sheath tumors (MPNSTs).10,23 Fluorescent in situ hybridization analysis of INI-1 demonstrated that 5 of 7 tested cases showed hemizygous deletion of INI-1 in at least a large subset of, if not most, cells.10 This is in contrast to the homozygous deletion seen in epithelioid sarcoma.24,25 Cases described with PHF1-TFE3 fusions also show diffuse and strong nuclear positivity for TFE3.12 S100 protein is a less reliable marker in cases lacking PHF1-EP400.12

Figure 2. Immunohistochemical findings in ossifying fibromyxoid tumor (OFMT; A) include positive staining with S100 protein in 75% of cases, which is more common in typical OFMT (B). About 25% of cases also show immunoreactivity for desmin (C), whereas essentially all tumors are negative for SOX10 (D) (hematoxylin-eosin, original magnification ×100 [A]; S100, original magnification ×100 [B]; original magnification ×100 [C and D]).
PROGNOSIS AND TREATMENT

Ossifying fibromyxoid tumors are typically treated by local excision and postsurgical surveillance if negative margins are achieved. Most authors agree that adjuvant radiation treatment is not indicated at the primary tumor site, recommending close surveillance and surgical excision of local recurrences or metastasis (metastatectomy) if possible, although no standard management has been published. Consideration for adjuvant radiation therapy should be reserved for those cases demonstrating malignant features, namely a combination of either high nuclear grade or hypercellularity with mitotic activity greater than 2 per 50 high-power fields.5,15 Adjuvant chemotherapy and radiation treatment efficacy has not been established, however, at least some clinicians in the literature have strongly advocated for radiotherapy.26 A single report of therapy response in lung metastases after chemotherapy (epirubicin plus ifosfamide) has been reported after metastatectomy, with partial response observed based on both radiology and histology examination.27 Although the risk of recurrence, metastasis, and death from disease is higher in cases with the above proposed malignant features, all OFMTs are considered to have malignant potential, not unlike solitary fibrous tumors. The overall reported metastatic rate of OFMTs classified as typical or atypical is 4% to 6%, whereas the combined metastatic rate in malignant cases is approximately 23%.5,10,14,15 Cutaneous tumors do not behave in a less aggressive fashion, and malignant classification should be interpreted using the same grading system.14

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for OFMT on histomorphologic grounds includes myoepithelial neoplasms, epithelioid nerve sheath tumors, low-grade fibromyxoid sarcoma, and sclerosing epithelioid fibrosarcoma. Other, rare differential diagnostic considerations might also include extraskeletal myxoid chondrosarcoma and EWSR1-NFATC2 sarcoma (not discussed herein).

Myoepithelial Neoplasms

Primary myoepithelial tumors of soft tissue present in a slightly younger age group on average, but with significant overlap, and they similarly are most common in the limb girdles and extremities.28 Microscopically, myoepithelial tumors share the low-power magnification lobularity and circumscription, but they are less likely to have a dense, fibrous capsule. Similar to OFMT, the constituent cells are often epithelioid and set within a chondromyxoid stroma, often in a mixed corded, reticular, and nested growth pattern, although a reticular pattern is much more common in myoepithelial tumors (Figure 3, A and B). Features that support myoepithelial differentiation include any overt ductal differentiation and prominent plasmacytoid morphology. Osseous metaplasia is seen in up to 10% to 15% of cases,
more commonly within the tumor than as a peripheral shell of bone. In contrast to OFMT, cytologic atypia is the sole criteria for malignancy in myoepithelial tumors, separating myoepitheliomas from myoepithelial carcinomas (Figure 3, C and D). In morphologically ambiguous cases, differentiation from OFMT can be established by demonstrating cytokeratin positivity, because myoepithelial tumors are positive for cytokeratin AE1/AE3 or CAM5.2 in more than 90% of cases.29 Similar rates of S100 protein positivity are seen between both entities, but in contrast to OFMT, SOX10 positivity is present in most myoepitheliomas (about 80%) and a subset of myoepithelial carcinomas (30%).22

**Epithelioid Schwannoma**

Because of the combination of epithelioid morphology within a mixed collagenous and myxoid stroma and S100 expression, epithelioid schwannomas can often enter the differential diagnosis of OFMT, particularly in superficial cases where epithelioid schwannomas are typically found. Epithelioid schwannomas are usually sharply circumscribed with a thin, perineural capsule, and cells are arranged in sheets or nests, less commonly showing a corded or trabecular pattern (Figure 4, A). Like typical schwannomas, hyalinized ectatic vessels are present in most cases (Figure 4, B), although these can also be prominent in a small proportion of OFMT. By definition epithelioid schwannomas show greater than 50% epithelioid cytomorphology; however, spindle cell features are seen in approximately one-third of cases.30 Giant collagen rosettes are present in a little more than 10% of cases, a feature which has rarely been described in OFMT. Osseous metaplasia has not been described in epithelioid schwannoma. In contrast to typical OFMT cases, epithelioid schwannoma cells commonly contain more irregular nuclei with reniform features or convoluted nuclear contours (Figure 4, D). Features of “degenerative atypia,” with large, smudgy nuclei, are seen in about one-third of cases. Cases with significant nuclear atypia and mitoses greater than 3 per 10 high-power fields that fall short of a diagnosis of epithelioid MPNSTs are “atypical variants” with prognosis identical to that of typical schwannomas. Immunohistochemical features that favor OFMT include the presence of desmin positivity or positivity for S100 protein significantly outweighing SOX10 expression, whereas features that favor epithelioid schwannoma include diffuse immunoreactivity for SOX10 or the presence of EMA or GLUT1 perineural cells within the fibrous capsule (Figure 4, C and D).22,30,31 Loss of INI-1 expression is seen in nearly half of epithelioid schwannomas (24 of 57; 42%) and correlates with inactivating mutations in SMARCB1.23,31

**Figure 4.** Epithelioid schwannomas are usually sharply circumscribed with a thin, perineural capsule, and cells are arranged in sheets or nests within a neurofibrillary stroma (A). The nuclei often exhibit reniform features or convoluted nuclear contours, and hyalinized ectatic vessels are present in many cases (B). The constituent cells exhibit less-defined cell borders compared with ossifying fibromyxoid tumor, and they are less likely to be arranged in a corded or trabecular pattern. The cells are diffusely positive for SOX10 (C), and the perineural capsule is highlighted by epithelial membrane antigen (D). Epithelioid malignant peripheral nerve sheath tumors (MPNSTs) exhibit lobular growth with high-grade cytologic features (E). High-power magnification demonstrates large, round vesicular nuclei with prominent nucleoli and frequent mitoses (F). They are more likely to show diffuse S100 expression than either conventional MPNSTs or ossifying fibromyxoid tumors (G), and most cases also show loss of INI-1 expression (H) (hematoxylin-eosin, original magnifications ×200 [A and E] and ×400 [B and F]; original magnification ×200 [C, D, G, and H]).
Epithelioid MPNST

Also in the differential diagnosis are epithelioid MPNSTs. Like epithelioid schwannomas, epithelioid MPNSTs are often superficial tumors, most commonly based in the subcutis of the lower extremities, and they can show at least focal spindling in one-third of cases, as well as association with a nerve or a component of epithelioid or conventional schwannoma in about 20% of cases.32 Most epithelioid MPNSTs exhibit lobular growth with high-grade cytologic features, including large vesicular nuclei with prominent nucleoli and frequent mitoses, and more than one-fourth of tumors exhibit necrosis (Figure 4, E and F). Rare chondro-osseous differentiation has been reported.32 In contrast to conventional MPNST, epithelioid MPNSTs show diffuse and strong S100 protein positivity in nearly 90% of cases, which is a greater proportion and intensity than malignant OFMT (Figure 4, G).32 Similarly, epithelioid MPNSTs appear to exhibit diffuse, strong nuclear SOX10 immunoreactivity, although this is not as well studied.23,33 Compared to conventional MPNSTs, epithelioid MPNSTs show a much lower association with neurofibromatosis type 1 (NF1), and in wild-type epithelioid MPNSTs, nearly all show inactivation mutations of SMARCB1, which strongly correlates with loss of INI-1 expression (Figure 4, H).32 This is in contrast to the patchy loss of expression seen in some cases of OFMT, correlating with hemizygous deletions. In cases of ambiguous INI-1 loss, confirmatory fluorescence in situ hybridization or sequencing can be considered. Recent literature has suggested loss of trimethylation of lysine 7 of histone H3 (H3K27me3) by immunohistochemistry can be useful in distinguishing MPNST from benign nerve sheath tumors; however, almost all tested epithelioid MPNSTs in the multiple cohorts showed retained H3K27me3.34–37

Low-Grade Fibromyxoid Sarcoma

Low-grade fibromyxoid sarcomas are typically composed of bland spindle cells in a predominantly collagenous matrix with areas of myxoid change (A); however, some examples are more cellular, with a greater degree of epithelioid morphology (B and C). Sclerosing epithelioid fibrosarcoma (SEF) is often variably cellular and consists of sheets and nests of monotonous epithelioid cells with clear cytoplasm and nuclear hyperchromasia in a dense hyalinized collagenous matrix (D and E). Approximately 80% of SEFs show diffuse and strong granular cytoplasmic positivity for MUC4 (F) (hematoxylin-eosin, original magnifications ×200 [A and B], ×400 [C and E], and ×100 [D]; original magnification ×400 [F]).
Sclerosing Epithelioid Fibrosarcoma

Sclerosing epithelioid fibrosarcoma is a rare malignant mesenchymal fibroblastic neoplasm that shares many clinical and morphologic features with both OFMT and LGFMS. Sclerosing epithelioid fibrosarcoma involves the deep soft tissues of the proximal extremities most commonly, followed by trunk and head and neck sites, but it affects an older age group more in line with OFMT, and it has a more aggressive clinical course than either LGFMS or OFMT. Local recurrences occur in about 50% of cases, whereas eventual distant metastases arise in about 60% of cases. Microscopically, SEF consists of sheets, nests, and cords of monotonous epithelioid cells with clear cytoplasm and nuclear hyperchromasia in a dense, hyalinized collagenous matrix (Figure 5, D and E). Dilated, hemangiopericytoma-like vessels are occasionally present. Like OFMT, both osseous metaplasia developing from the hyaline matrix and myxoid change have been reported, but only in a small subset of cases.

Similar to LGFMS and OFMT, SEF is associated with recurrent fusion events, although the partners are more heterogeneous. Some cases of SEF show both genetic and histologic overlap with LGFMS. Most SEF tumors harbor a recurrent EWSR1-CREB3L1 fusion, with less common fusion events including EWSR1-CREB3L2 and FUS-CREB3L2. Indeed, a subset of SEF cases show mixed morphology of LGFMS and SEF within the primary tumor and are designated “synchronous hybrid SEF/LGFMS,” which are more likely to harbor a t(7;16) (q33;p11) FUS-CREB3L1 fusion. Additionally, late recurrences and metastases of LGFMS have a tendency to exhibit morphology in line with SEF, described as “metachronous hybrid SEF/LGFMS.” Thus, recurrent EWSR1-CREB3L1 fusions are most common in “pure” SEF, whereas hybrid cases are enriched for other fusions seen in LGFMS. A study of pure SEFs and hybrid SEF/LGFMS using comprehensive genomic and transcriptomic analysis found that hybrid cases likely result from acquisition of secondary genomic alterations, given that LGFMS shows a relatively low degree of genomic imbalances compared with pure SEF and hybrid SEF/LGFMS. This correlates with the observation that both pure SEF and hybrid SEF/LGFMS follow a more aggressive clinical course than conventional LGFMS.

By immunohistochemistry, like LGFMS, most SEFs show diffuse and strong cytoplasmic positivity for MUC4 (Figure 5, F), albeit a lower proportion of nearly 80% of cases, which includes the hybrid LGFMS-SEF features, which are nearly always immunoreactive. Excluding hybrid cases, about 70% of cases are positive. EMA positivity is seen in about half of cases, and focal S100 and cytokeratin positivity can be seen in up to 40% and 30% of cases, respectively, but SEFs are typically negative for desmin.

CONCLUSIONS

Ossifying fibromyxoid tumor is predominantly a subcutaneous soft tissue tumor of uncertain histogenesis and intermediate malignant potential, which can be difficult to correctly diagnose given its rarity and somewhat variable histology and immunophenotype. Although initial suggestions were made that OFMT exhibited a modified myoepithelial or nerve sheath derivation, the discovery of a recurrent translocation in the vast majority of tumors has helped to place this entity into the category of soft tissue tumors with recurrent translocations lacking a distinct histogenesis, similar to synovial sarcoma. Initial reports of cases with malignant histologic features and aggressive behavior classified as OFMT because of a background of more conventional OFMT have been supported through the molecular characterization of recurrent PHF1 rearrangements, which has also expanded this entity’s spectrum of morphology. Genetic alterations leading to this malignant “transformation” have yet to be described, but histologic features of increased mitotic activity of more than 2 per 50 high-power fields and high cellularity or nuclear atypia have been accepted as being predictive of an increased risk of aggressive behavior. Despite these predictive features, the rarity of the tumor has precluded an established treatment standard other than primary excision with negative margins, and in the limited published anecdotal literature, chemotherapy and radiation are most commonly reserved for recurrent or metastatic disease. A combination of at least focally classic morphology and immunoreactivity can lead to the diagnosis in most cases, but a high index of suspicion with exclusion of other entities in the histologic differential diagnosis by a limited panel of immunohistochemical stains can guide ancillary testing for PHF1 alterations (either by fluorescence in situ hybridization or targeted next-generation sequencing) in atypical cases.

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with pathologic comparison.


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