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Review Article

Deciphering an Uncommon Soft-Tissue Entity Through Morphologic Patterns, Diagnostic Challenges, and Genetic Alterations

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Abstract

Ossifying fibromyxoid tumor (OFMT) is an uncommon soft-tissue neoplasm characterized by distinctive structural features and a variable clinical course. Although conventionally associated with a well-defined lobulated architecture and peripheral bone formation, its microscopic appearance can differ considerably between individual cases. These variations may create diagnostic difficulties, particularly when cellular atypia, increased mitotic activity, unusual stromal composition, or loss of characteristic immunohistochemical markers is encountered. Clinical manifestations generally include a slowly enlarging, painless soft-tissue mass, although uncommon anatomical locations and aggressive presentations have also been documented. Histopathological examination remains central to diagnosis, supported by immunohistochemical assessment and molecular investigations. Recurrent alterations involving PHF1 and its fusion partners provide important diagnostic evidence and offer insight into the epigenetic mechanisms associated with tumor development. Distinguishing OFMT from other myxoid, ossifying, neural, and fibroblastic neoplasms is essential because these entities may differ substantially in biological behavior and clinical management. This review examines the available evidence concerning the clinical presentation, morphological spectrum, histogenesis, immunophenotype, genetic alterations, differential diagnosis, and prognostic characteristics of OFMT. An integrated pathological and molecular evaluation provides the strongest foundation for accurate classification and appropriate patient management.

Keywords: Ossifying Fibromyxoid Tumor; Mesenchymal Neoplasms; Soft Tissue Pathology; Histomorphology; PHF1 Rearrangement; Molecular Genetics; Immunohistochemistry; Differential Diagnosis; Sarcoma Classification

INTRODUCTION

Ossifying fibromyxoid tumor (OFMT) represents a rare mesenchymal tumor of soft tissue, generally classified among tumors with uncertain histogenetic differentiation. Its characteristic combination of fibrous, myxoid, and osseous components makes it a distinctive entity within soft-tissue pathology. The current classification recognizes its variable biological potential, ranging from lesions with indolent behavior to tumors demonstrating histological features associated with malignancy [1].

The entity was originally characterized through a clinicopathological series describing its distinctive cellular arrangement, myxoid stromal background, and peripheral metaplastic bone formation [2]. Subsequent investigations have demonstrated that this appearance is not universal. Certain tumors display unusual combinations of collagenous stroma, clear-cell morphology, cartilaginous differentiation, and atypical cellular arrangements, creating substantial overlap with other mesenchymal lesions [3].

The diagnostic significance of these variations extends

beyond morphological classification. Some lesions exhibit increased cellularity, prominent nuclear atypia, and elevated mitotic activity, features associated with local recurrence and metastatic progression. The absence of conventional morphological characteristics in such cases may further complicate identification.

Molecular investigations have expanded the understanding of OFMT by identifying recurrent chromosomal rearrangements, especially those involving PHF1. These alterations have established a connection between the tumor's morphological characteristics and abnormalities affecting epigenetic regulation. Nevertheless, molecular findings must be interpreted alongside microscopic and immunohistochemical observations. A clear understanding of the clinical, histological, and genetic spectrum is therefore necessary to distinguish OFMT from its morphological mimics. This review brings together findings from the published literature to discuss its clinical characteristics, pathological variations, molecular background, diagnostic evaluation, and prognostic implications.

LITERATURE REVIEW

Clinical Presentation and Anatomical Distribution

OFMT is generally encountered in adults and most frequently develops within the superficial soft tissues. Patients commonly present with a localized swelling that enlarges gradually over an extended period. Pain and functional impairment are uncommon during the initial stages, and the lesion may remain unnoticed until it becomes sufficiently prominent. A clinicopathological investigation involving 104 tumors demonstrated that middle-aged individuals represented a substantial proportion of affected patients, with a greater frequency among males [4]. Additional clinicopathological and genomic observations have supported the broad clinical and biological variability of this neoplasm [5].

Although the extremities represent the predominant anatomical distribution, OFMT has been identified in several less frequently affected regions. Orbital involvement is an example of an unusual presentation in which the lesion may resemble other space-occupying soft-tissue abnormalities [6]. Tumors arising in the parapharyngeal region can demonstrate aggressive characteristics and create difficulties during anatomical assessment and surgical planning [7]. Oral involvement has also been documented, including lesions developing within the mandibular gingiva and posterior oral cavity. These presentations may initially resemble more common odontogenic or oral soft-tissue lesions, making histopathological examination essential for confirmation [8,9].

Intracranial and spinal presentations represent uncommon but clinically significant manifestations. Intracranial lesions can resemble meningioma or other primary central nervous system neoplasms, while malignant

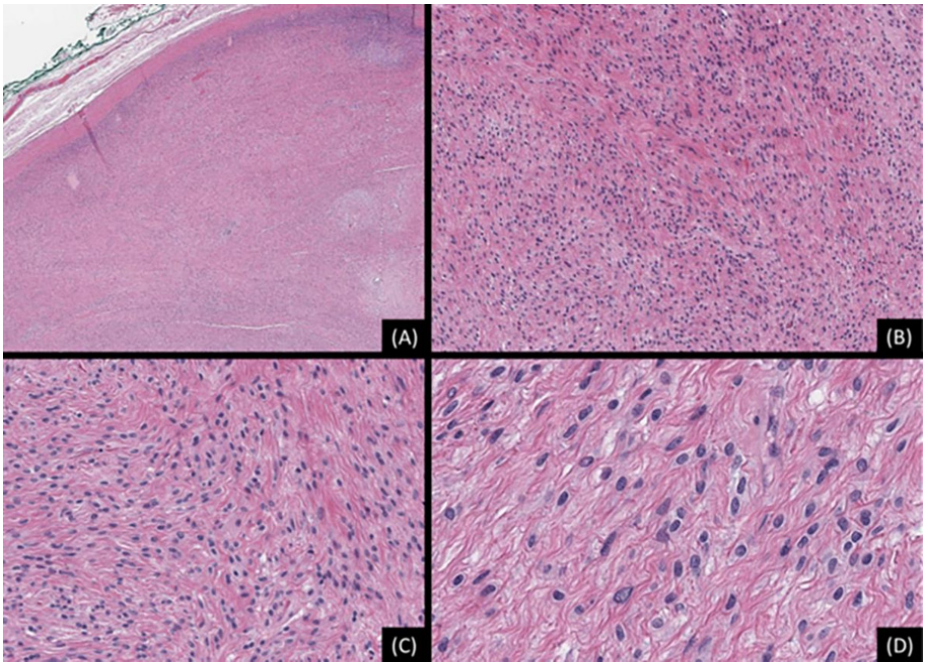


Figure 1: Representative Histopathological Features of Ossifying Fibromyxoid Tumor.

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tumors involving the paraspinal region may extend into adjacent spinal structures [10,11]. Additional reports have documented tumors arising in the retroperitoneum, breast, and genitourinary system. These unusual locations broaden the differential diagnosis and demonstrate that the tumor is not restricted to the superficial tissues of the extremities.

Gross and Radiological Characteristics

On gross examination, OFMT commonly appears as a circumscribed, rounded or oval mass with a firm or rubbery consistency. The cut surface generally displays a whitish appearance, sometimes accompanied by a glistening or gelatinous central region. A peripheral shell of mineralized tissue may be identified (Figure 1), reflecting the characteristic osseous component of the lesion [12–14].

Radiological examination can reveal peripheral mineralization or an irregular ossified margin. These findings may assist in identifying the lesion before surgery, although imaging alone is insufficient to establish a definitive diagnosis. The degree and distribution of mineralization can vary substantially, and some tumors show little or no recognizable peripheral ossification [15].

The presence of prominent mineralized tissue may create diagnostic overlap with surface-based bone tumors, particularly parosteal osteosarcoma. Evaluation of the lesion's relationship to adjacent bone, together with its internal architecture and histological composition, helps distinguish these entities [16].

Histopathological Spectrum and Biological Behavior

The conventional microscopic appearance is characterized by a lobulated or multilobulated growth pattern. Rounded to oval tumor cells are generally arranged in nests, short cords, trabeculae, or sheets within a collagenous and myxoid extracellular matrix. The peripheral region frequently contains mature metaplastic bone, although its distribution and completeness differ among individual tumors. Perivascular hyalinization and a fibrous pseudocapsule may also be observed. Morphological variation is a major feature of OFMT and can complicate classification when conventional architectural characteristics are absent. A detailed pathological review has described the broad range of cellular arrangements, stromal patterns, and genetic characteristics that contribute to this diagnostic complexity [17].

Certain lesions demonstrate extensive cellularity, nuclear enlargement, irregular nuclear contours, and increased mitotic activity. Other unusual findings include clear-cell transformation, cartilage-like differentiation, collagen entrapment, and prominent osteoid deposition. Such appearances can result in an initial interpretation of a different mesenchymal malignancy. Molecularly investigated examples have demonstrated that tumors resembling osteosarcoma may nevertheless belong to the OFMT spectrum [18].

The variation in histological appearance has also been documented across case series describing unusual architectural and stromal findings. These observations emphasize that the absence of a conventional peripheral bony shell does not automatically exclude the diagnosis [19]. Biological behavior ranges from relatively indolent lesions to tumors with local recurrence and distant dissemination. Malignant examples may demonstrate infiltrative margins, marked nuclear atypia, elevated proliferative activity, and necrotic areas. The lungs are among the documented sites of distant spread. Rare metastatic cases have demonstrated extensive involvement of thoracic structures, illustrating the potential clinical consequences of aggressive tumor behavior [20].

A separate examination of atypical and malignant examples demonstrated substantial variation in cellular composition and mitotic characteristics. These findings support assessment of several histological parameters rather than relying on a single microscopic feature when estimating biological risk [21]. Repeated recurrence can occasionally be accompanied by secondary sarcomatous differentiation, including the development of an osteosarcomatous component, although such events remain uncommon [22].

Histogenesis and Cellular Differentiation

The precise cell of origin of OFMT remains unresolved. Earlier interpretations proposed a relationship with peripheral nerve-associated cells because many tumors demonstrate S100 immunoreactivity. However, the variable expression of neural markers and the presence of other differentiation patterns have made a purely neural origin difficult to establish.

Ultrastructural examinations have identified similarities between OFMT and myoepithelial neoplasms. These observations include intermediate filaments, basal-lamina-like material, and cellular characteristics associated with myoepithelial differentiation. Such findings support the possibility of a relationship with the myoepithelial lineage, although they do not conclusively establish the histogenesis of every tumor [23]. Additional ultrastructural

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Clinicopathological parameter	Characteristic findings	Atypical features and clinical significance
Age distribution	Predominantly affects middle-aged adults, with reported cases ranging from childhood to older age.	Pediatric and neonatal presentations are uncommon but documented.
Sex distribution	Slight male predominance has been reported in several clinical series.	The sex distribution does not independently influence diagnosis or prognosis.
Clinical presentation	Usually presents as a slowly enlarging, painless, localized soft-tissue mass.	Long-standing lesions may remain clinically unnoticed before diagnosis.
Anatomical distribution	Most frequently occurs in the superficial soft tissues of the extremities.	Head and neck, intracranial, spinal, paraspinal, retroperitoneal, breast, and genitourinary locations have also been described.
Tumor size	Commonly measures approximately 3–5 cm.	Larger tumors measuring more than 10 cm have occasionally been reported.
Gross appearance	Usually well-circumscribed, oval or rounded, and firm to rubbery, with a whitish or glistening cut surface.	Peripheral mineralization may be absent or incomplete in a proportion of cases.
Radiological characteristics	May demonstrate peripheral ossification and a well-defined soft-tissue mass.	Extensive mineralization can create radiological overlap with parosteal osteosarcoma.
Conventional histology	Multilobulated architecture, uniform epithelioid cells, and collagenous or fibromyxoid stromal components.	Architectural variation may complicate recognition in limited tissue specimens.
Peripheral ossification	Metaplastic lamellar or woven bone commonly forms a peripheral shell around the tumor.	Absence of peripheral ossification does not exclude OFMT.
Cellular morphology	Tumor cells generally have round to oval nuclei, pale to eosinophilic cytoplasm, and inconspicuous nucleoli.	Clear-cell changes, binucleation, nuclear atypia, and spindle-cell morphology may occur.
Stromal characteristics	Fibromyxoid or collagenous matrix with variable perivascular hyalinization.	Chondroid differentiation, collagen entrapment, mucinous changes, and reduced myxoid matrix may be present.
Mitotic activity	Usually low in conventional tumors.	Increased mitotic activity, particularly when accompanied by nuclear atypia and hypercellularity, raises concern for malignant behavior.
Atypical or malignant morphology	May demonstrate increased cellularity, nuclear pleomorphism, infiltrative growth, and necrosis.	These characteristics are associated with a greater risk of local recurrence and metastatic progression.

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Metastatic potential	Conventional tumors generally exhibit relatively indolent behavior.	Malignant variants may metastasize, most frequently to the lungs.
Treatment	Surgical excision is the principal treatment for localized tumors.	Wider excision and additional oncological management may be required for aggressive or recurrent lesions.
Prognosis and follow-up	Clinical outcome is generally favorable for conventional tumors.	Long-term surveillance is advisable because recurrence and distant metastasis can occur in malignant variants.

Table 1: Clinicopathological Characteristics of OFMT Across Its Morphological Spectrum.

Abbreviations: OFMT, Ossifying Fibromyxoid Tumor.

investigations have demonstrated consistent structural characteristics despite considerable differences in immunohistochemical expression. This distinction suggests that OFMT may represent a biologically related group of lesions with variable phenotypic differentiation [24].

Cytological Characteristics

Fine-needle aspiration and other cytological techniques can provide preliminary information about an unidentified soft-tissue mass. Nevertheless, OFMT may be difficult to recognize in cytological preparations because its cellular component can resemble several other mesenchymal lesions.

Smears may contain isolated tumor cells, small cohesive groups, and fragments of myxoid or fibrillary extracellular material. The identification of osteoid-like material, when present, can provide an additional diagnostic clue. However, the quantity of matrix obtained through aspiration may be insufficient to demonstrate the complete architecture of the lesion. Reported cytological observations have highlighted the diagnostic difficulties associated with isolated epithelioid cells and limited background material. Correlation with clinical findings and subsequent histological examination is therefore important [25]. Malignant variants may display more prominent nuclear abnormalities, including enlarged nuclei, irregular contours, coarse chromatin, and conspicuous nucleoli. Increased cellular atypia can raise suspicion of an aggressive lesion, although cytological findings alone cannot reliably establish its final biological classification [26].

Additional case-based investigations have demonstrated the value of identifying characteristic extracellular material and combining cytological observations with tissue-based assessment. Histological confirmation remains necessary when the initial specimen does not adequately represent the tumor architecture (Table 1)[27].

Immunohistochemical Profile

Immunohistochemistry provides valuable supplementary evidence when distinguishing OFMT from other mesenchymal neoplasms. S100 protein is frequently expressed, although its distribution and intensity can vary. Desmin may also be detected, while other markers associated with neural or myoepithelial differentiation can show variable reactivity. The immunophenotype should not be interpreted independently of morphology. Some tumors retain characteristic staining patterns, whereas atypical and malignant examples may demonstrate reduced or absent expression of markers normally associated with conventional OFMT. PHF1-associated molecular alterations have been linked to distinct immunohistochemical findings. In particular, tumors containing PHF1::TFE3 rearrangements can demonstrate nuclear TFE3 expression, providing a useful clue that may direct further genetic investigations [28].

Immunohistochemical findings in malignant superficial lesions can be particularly variable. The presence of unusual fusion events may coincide with an altered protein-expression profile, making a broad diagnostic panel more informative than reliance on individual markers (Table 2) [29].

Molecular Alterations and Genetic Basis

The molecular understanding of OFMT has advanced substantially through investigations of chromosomal rearrangements and gene-fusion events. These studies indicate that abnormal chromatin regulation is an

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Category	Marker or molecular alteration	Characteristic findings	Diagnostic significance
Immunohistochemistry	S100 protein	Frequently positive in conventional tumors.	Supports the diagnosis, although expression may be weak, focal, or absent in malignant variants.
Immunohistochemistry	Desmin	Frequently expressed in a proportion of cases.	Provides additional support for OFMT when interpreted with morphological findings.
Immunohistochemistry	EAAT4	Frequently positive.	Useful supplementary immunohistochemical marker.
Immunohistochemistry	Neurofilament and CD56	May demonstrate positive staining.	Reflects the variable neural-associated immunophenotype.
Immunohistochemistry	CD10 and INSM1	Expression has been reported.	May provide additional diagnostic information in selected cases.
Immunohistochemistry	INI1	Often demonstrates mosaic expression.	Associated with underlying SMARCB1 alterations, including chromosome 22q loss.
Immunohistochemistry	TFE3	Nuclear expression may occur in tumors with PHF1::TFE3 fusion.	May indicate a specific underlying molecular alteration.
Immunohistochemistry	Keratins, EMA, GFAP, SMA, CD99, and collagen IV	Variable or occasional expression.	These findings should not be considered independently diagnostic.
Immunohistochemistry	HMB45, CD34, SOX10, and PRAME	Generally negative.	Helps narrow the differential diagnosis in the appropriate pathological context.
Immunohistochemistry	ER and PR	Expression has been reported in selected cases.	Uncommon findings that may occur in tumors with specific molecular alterations.
Immunohistochemistry	Pan-TRK	Reported in selected BCOR-rearranged OFMTs.	Requires molecular correlation; immunoreactivity alone does not establish an NTRK fusion.
Molecular genetics	PHF1 rearrangements	Identified in approximately 80%–85% of tumors.	Represents the major recurrent molecular alteration associated with OFMT.

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Molecular genetics	EP400::PHF1	One of the most commonly reported PHF1-associated fusions.	Important molecular finding supporting tumor classification.
Molecular genetics	Other PHF1 fusion partners	EPC1, MEAF6, TFE3, FOXR1, FOXR2, CREBZF, TP53, and JAZF1.	Demonstrates the molecular heterogeneity of OFMT.
Molecular genetics	Non-PHF1 fusion events	MEAF6::SUZ12, EPC1::SUZ12, CREBBP::BCORL1, KDM2A::WWTR1, ZC3H7B::BCOR, CSMD1::MEAF6, and EPC1::PHC1.	Identifies alternative molecular pathways associated with OFMT.
Molecular genetics	BCOR internal tandem duplication	Rarely reported in malignant OFMT.	Represents an additional molecular alteration requiring further investigation.
Molecular genetics	SMARCB1 alteration	Hemizygous deletion involving chromosome 22 or 22q may occur.	Corresponds to the mosaic INI1 immunohistochemical pattern.
Molecular genetics	RB1 loss	Reported in approximately one-third of cases, particularly atypical and malignant tumors.	May be associated with more aggressive pathological characteristics.
Molecular mechanism	PRC2-associated chromatin regulation	PHF1 participates in polycomb-related epigenetic regulation and histone modification.	Abnormal fusion-associated activity may disrupt normal transcriptional control.
Molecular testing	PHF1 break-apart FISH	Detects rearrangements involving the PHF1 locus.	Useful initial molecular investigation in morphologically suspicious cases.
Molecular testing	Targeted RNA sequencing and NGS	Can identify established and uncommon gene-fusion events.	Particularly useful when FISH is negative or the morphology and immunophenotype are atypical.

Table 2: Immunohistochemical and Molecular Features Relevant to OFMT Classification.

Abbreviations: EAAT4, Excitatory Amino Acid Transporter 4; EMA, Epithelial Membrane Antigen; ER, Estrogen Receptor; FISH, Fluorescence In Situ Hybridization; GFAP, Glial Fibrillary Acidic Protein; INI1, Integrase Interactor 1; INSM1, Insulinoma-Associated Protein 1; NGS, Next-Generation Sequencing; OFMT, Ossifying 99 Tumor; PR, Progesterone Receptor; PRAME, Preferentially Expressed Antigen in Melanoma; PRC2, Polycomb Repressive Complex 2; RB1, Retinoblastoma 1; SMA, Smooth Muscle Actin; SMARCB1, SWI/SNF Related Matrix Associated Actin Dependent Regulator of Chromatin Subfamily B Member 1.

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important component of tumor development. Recurrent translocations in sarcomas have been associated with changes in the localization of chromatin-modifying complexes, providing a broader biological explanation for fusion-driven oncogenesis [30]. In OFMT, PHF1-associated alterations represent a central molecular feature. Research examining gene-expression patterns and chromatin accessibility has demonstrated that PHF1 fusions are associated with distinct molecular profiles compared with non-neoplastic mesenchymal cells. These findings support an important role for altered epigenetic regulation in the development and maintenance of the tumor [31].

Additional molecular investigations have identified altered expression of neurotrophic receptor-related proteins in selected fusion-associated sarcomas. Such findings have generated interest in the interpretation of pan-tropomyosin receptor kinase staining, especially when evaluating rare mesenchymal lesions with overlapping molecular characteristics [32]. A directly documented example of BCOR-rearranged malignant OFMT demonstrated pan-TRK immunoreactivity, illustrating a potential diagnostic complication when interpreting molecularly influenced protein expression [33]. Reduced or absent S100 expression has also been documented in malignant tumors, indicating that the lack of conventional neural-marker positivity should not independently exclude OFMT [34].

Chromosomal abnormalities and PHF1 rearrangements

Early cytogenetic studies identified structural and numerical chromosomal abnormalities in OFMT. Reported findings include clonal chromosomal changes, unbalanced rearrangements, and complex karyotypic patterns. The identification of these alterations provided the foundation for subsequent investigations into specific oncogenic events [35–37].

Recurrent rearrangement of PHF1 was subsequently established as an important molecular characteristic of OFMT. PHF1 encodes a protein associated with polycomb-mediated chromatin modification and participates in the regulation of developmental gene expression. Rearrangements involving this gene can disrupt normal epigenetic control and contribute to abnormal transcriptional activity [38]. EP400 represents one of the recognized fusion partners of PHF1. The identification of the EP400::PHF1 fusion established an important connection between chromosomal rearrangement and the molecular classification of OFMT [39]. Further investigations have identified additional fusion partners, including MEAF6, EPC1, and BCOR-associated alterations. These discoveries demonstrate that the genetic landscape is not restricted to one recurrent rearrangement and that multiple molecular pathways can contribute to a similar morphological phenotype [40].

More recently characterized fusion events involving FOXR1 and FOXR2 have expanded the recognized molecular diversity of malignant OFMT. These alterations have been documented in tumors displaying atypical or aggressive morphological characteristics, suggesting that molecular variation may help explain some differences in biological behavior. Nevertheless, the presence of an uncommon fusion should be interpreted alongside the complete

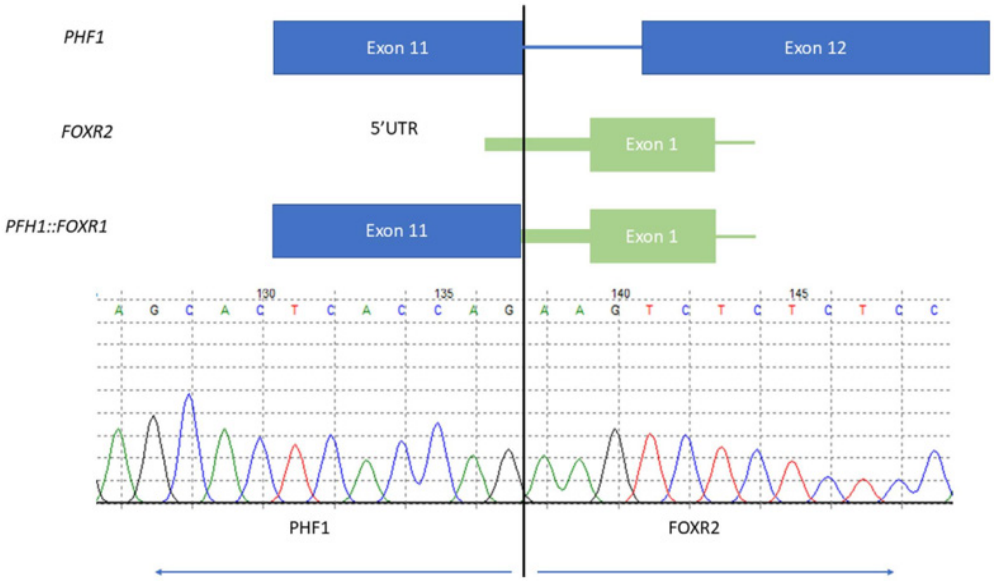


Figure 2: Molecular Alterations and PHF1-Associated Pathways in OFMT.

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pathological findings rather than treated as an independent marker of malignancy (Figure 2) [41].

Molecular Diagnostic Evaluation

Fluorescence in situ hybridization (FISH) has an established role in detecting chromosomal rearrangements associated with OFMT. PHF1 break-apart probes can provide evidence of gene disruption in tumors displaying compatible morphological characteristics. However, this technique does not necessarily identify the fusion partner, and certain complex or cryptic rearrangements may remain unresolved. A molecular investigation involving 41 tumors demonstrated the diagnostic value of PHF1 rearrangement testing, including in the evaluation of malignant variants. Such findings support the use of targeted molecular analysis when conventional pathological findings are inconclusive [42].

Molecular interpretation must also account for the relationship between morphological classification and clinical outcome. A clinicopathological analysis of subcutaneous lesions demonstrated that differences in tumor architecture, cellular characteristics, and proliferative activity contribute to diagnostic and prognostic assessment [43]. The differential diagnosis may include myoepithelial neoplasms, low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma, malignant peripheral nerve sheath tumor, and extraskeletal osteosarcoma. Myoepithelial tumors can demonstrate overlapping immunohistochemical features, while EWSR1-associated rearrangements provide useful evidence in selected cases. However, a negative result does not independently exclude a myoepithelial lesion [44].

Malignant peripheral nerve sheath tumor is another important diagnostic alternative. The evaluation of H3K27me3 can help distinguish this entity from selected histological mimics. Retained expression in OFMT and loss of staining in many malignant peripheral nerve sheath tumors can provide additional discriminatory information when interpreted in the appropriate morphological setting [45].

Treatment and Prognostic Considerations

Complete surgical removal remains the principal treatment approach for localized OFMT. The choice between marginal and wider excision depends on tumor location, size, anatomical relationships, and pathological characteristics. Local surveillance is important because recurrence may develop following initial treatment, including after an extended disease-free interval. Tumors showing increased mitotic activity, significant nuclear atypia, and high cellularity require careful assessment because these features have been associated with less favorable outcomes. A clinicopathological study of atypical and malignant variants highlighted the importance of identifying aggressive histological characteristics when determining the likely clinical course [46].

The management of metastatic disease is more complex because the available evidence is largely derived from individual cases and small clinical series. Surgical treatment of selected metastatic deposits, radiotherapy, and systemic chemotherapy have been reported in patients with advanced disease. A published metastatic case demonstrated a response to regional perfusion and combination chemotherapy, although such observations cannot establish a standard treatment protocol for this rare neoplasm [47].

Long-term follow-up is appropriate because the rarity of OFMT limits the availability of large prospective studies. Prognostic assessment should integrate histological grade, mitotic activity, necrosis, local growth pattern, resection status, and evidence of distant dissemination.

CONCLUSION

OFMT remains a diagnostically demanding mesenchymal neoplasm because its morphology and immunophenotype vary widely across cases. Although conventional lesions often show a lobulated arrangement of epithelioid cells, fibromyxoid stroma, and peripheral ossification, atypical tumors may lack several of these defining features. Histological assessment is therefore central to classification, while immunohistochemistry and molecular testing provide additional evidence when the findings overlap with other soft-tissue tumors. PHF1-related rearrangements and other fusion events have clarified important aspects of tumor biology, particularly the contribution of altered chromatin regulation. Nevertheless, molecular findings should be interpreted with the clinical presentation and microscopic characteristics rather than used in isolation. Recognition of aggressive features, including increased cellularity, nuclear atypia, mitotic activity, and infiltrative growth, is important for prognostic assessment. Complete excision and appropriate long-term surveillance remain central to management. Continued accumulation of well-documented cases and molecular data will improve diagnostic consistency and strengthen understanding of the clinical behavior of this uncommon neoplasm.

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