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Chapter 12

EWSR1-SMAD3-Positive Fibroblastic Tumor: A New Frontier in Tumor Pathology

Parth Goswami[1], Rushang Dave[2*] and Sonagara NikhilKumar Mavjibhai[3]

[1]*Assistant Professor, All India Institute Of Medical Sciences, Rajkot, Gujarat, India.*
[2]*Assistant Professor, Shantabaa Medical College And Hospital, Amreli, Gujarat, India*
[3]*Pathologist, Military hospital Jaipur, Rajasthan, India*
[*]*Corresponding Author.*

Abstract

The EWSR1-SMAD3-positive fibroblastic tumor is recently added to the fifth edition of the WHO Classification of Soft Tissue Tumors. This rare tumor is formed by t(22;15)(q12;q21) translocation. That leads to the formation of the EWSR1-SMAD3 fusion gene. TGF B/SMAD signaling pathway disrupts results in tumorigenesis. Only 15 cases have been reported till date. Tumors are most commonly located on soft tissue extremities. Tumors have low malignant potential and locally recur if not effectively removed. Diagnosis based on FISH, RT-PCR, and NGS. Future research should focus on unraveling the oncogenic mechanisms of the EWSR1-SMAD3 fusion and exploring targeted therapies. This review shows molecular pathology in diagnosing and managing this emerging tumor entity.

Keywords: EWSR1-SMAD3-Positive fibroblastic tumor, Molecular diagnostics, Rare tumor, Soft tissue.

Introduction

Soft tissue neoplasms are known for their challenging diagnosis due to varying lines of differentiation. Accurate diagnosis is essential for determining appropriate treatment and prognosis. Previous WHO Classification categorizes Soft Tissue Tumors based on their histological differentiation. In the recent fifth edition (2020), several new entities have been introduced. The classification based on reflecting advancements in understanding biological behavior, genetics, and morphology. With the progress in molecular genetics, numerous novel recurrent genetic alterations detected and have been incorporated into this edition [1,2]. The field of molecular pathology has revolutionized the classification of soft tissue tumors by identifying rare subtypes defined by specific gene fusions [3]. One such entity is the EWSR1-SMAD3-positive fibroblastic tumor, recently classified in the fifth edition of the WHO Classification of Tumors of Soft Tissue and Bone [4]. With only 15 cases reported in the English literature, this emerging tumor type is distinguished by a recurrent EWSR1-SMAD3 gene fusion [5]. This review addresses the tumor's clinical characteristics, histological features, genetics, and implications for diagnosis and treatment.

Clinical Presentation

EWSR1-SMAD3-positive fibroblastic tumors predominantly occur in the soft tissues of the extremities, particularly the foot and hand. Patients present with a slow-growing, painless, well-defined mass. The tumor spans a wide age range (1–68 years). These tumors are more common in females. They are rare and usually occur in specific groups, such as children. The tumor size ranges from 1 to 2 cm. Most lesions are found in the dermis or subcutaneous tissue. While metastasis has not been reported, local recurrence occurs frequently, often attributed to incomplete excision [6].

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Histopathology

Histologically, the tumor consists of uniform spindle cells arranged in fascicular or storiform patterns. These cells are embedded in a collagenous to myxoid stroma. The stroma occasionally shows areas of hyalinization and myxoid changes. The nuclei of the cells are elongated, with fine chromatin and small, inconspicuous nucleoli. Mitotic activity is rare [7].

Underdiagnosing EWSR1-SMAD3-positive fibroblastic tumor can affect patient outcomes. This is because it has unique clinical and pathological features. Immunohistochemistry shows that the tumor is strongly positive for ERG. It lacks expression of S100, CD34, α -SMA, or other markers seen in other fibroblastic or muscle-related tumors. This pattern helps to differentiate it from similar tumors like low-grade fibromyxoid sarcoma and monophasic synovial sarcoma [7,8,9].

Molecular Pathogenesis

EWSR1 is most common among the various genes that can be rearranged in soft tissue neoplasms. EWSR1 binds with other genes to generate recurrent fusion genes. This leads to a spectrum of diverse mesenchymal and nonmesenchymal neoplasms. They manifest as small round cells, spindle cells, clear cell or adipocytic tumors, or tumors with distinctive myxoid stroma [10]. The EWSR1 (Ewing Sarcoma Breakpoint Region 1) gene is located on chromosome 22q12. The function is to encode a protein involved in RNA processing and transcription regulation [11]. On chromosome 15q22.33 a genetic material called SMAD3 is found. It codes for a protein that has the function of the TGF-β (Transforming Growth Factor Beta) signaling pathway [12]. These signals play a role in cell growth, differentiation, apoptosis, and the production of extracellular matrix [13,14]. A chromosomal translocation leads to EWSR1- SMAD3 fusion. This mixed protein changes how SMAD3 target genes are controlled during transcription. That leads to downstream signaling pathways to be activated in a way that isn't supposed to happen. The fusion protein might make these pathways more active or less active, leading to uncontrolled fibroblastic proliferation and the growth of tumors. This tumor is defined by the EWSR1-SMAD3 fusion gene. It results from a t(22;15)(q12;q21) translocation. This genetic change affects the TGF-β/SMAD signaling pathway. It leads to tumor formation by changing extracellular matrix production and fibroblast activity [8,9,15].

Molecular Diagnosis

During carcinogenesis, genetic and molecular alterations develop. By identifying them, molecular diagnostics help in cancer treatment. FISH remains a cornerstone diagnostic tool in modern molecular pathology. FISH bridges cytogenetics and molecular biology for personalized medicine. FISH probe identify EWSR1 gene rearrangement [5]. RTPCR is the best to find out chromosomal translocation that makes the fusion genes. Identify Fusions helps in target therapy in oncology [5,18]. NGS expands the understanding of cancer biology by identifying unknown fusions. Low Fusion transcripts can be detected by NGS in heterogeneous samples [19].

Differential Diagnosis

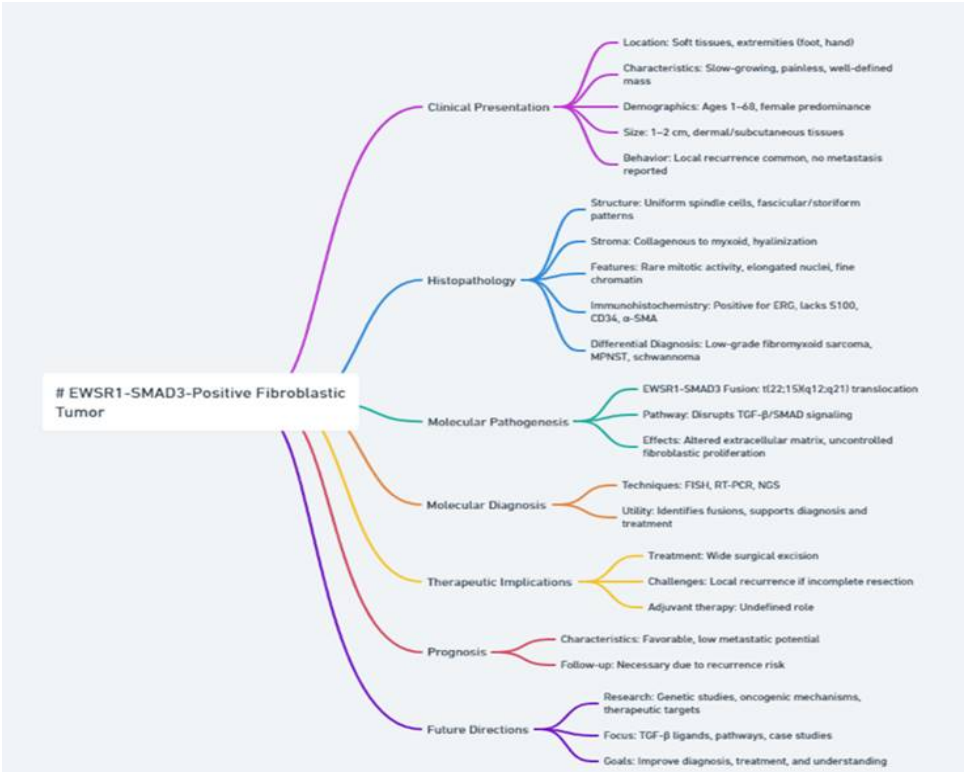

Figure 1: Overview of the clinicopathological and molecular characteristics of EWSR1–SMAD3-positive fibroblastic tumor

EWSR1-SMAD3-positive fibroblastic tumors needed to differentiate from other soft tissue tumors. Low-grade MPNST shows pronounced nuclear atypia and high mitotic figures. Cellular schwannoma can be differentiated by S100 protein. Low-grade fibromyxoid sarcoma shows expression of MUC4. Molecular marker SS18-SSX gene fusion helps to identify monophasic synovial sarcoma [9].

Challenges in Diagnosis

Diagnosing EWSR1-SMAD3-positive fibroblastic tumors can be challenging. EWSR1-SMAD3 tumors are similar to other fibroblastic tumors on histopathology. Immunohistochemistry helps but FISH and NGS are needed for confirmation. It is recently added. Many pathologists are unfamiliar leads to underdiagnosis or misclassification [9].

Therapeutic Implications

Wide surgical excision remains the cornerstone of treatment. While most cases are cured with complete resection, incomplete removal leads to local recurrence in up to 27% of cases. The role of adjuvant therapy, such as radiation or targeted therapies, remains undefined due to limited data [16].

Prognosis

EWSR1-SMAD3-positive fibroblastic tumors generally have a favorable prognosis, exhibiting indolent behavior and low metastatic potential. EWSR1-SMAD3-positive fibroblastic tumors exhibit low metastatic potential due to their intrinsic biological and molecular characteristics. However, long-term follow-up is necessary to monitor for recurrence, as evidenced by the recurrent case discussed in the literature [17].

Future Directions

Future research on EWSR1-SMAD3-positive fibroblastic tumors should focus on several key areas. Genetic studies are essential to uncover the oncogenic mechanisms of the EWSR1-SMAD3 fusion. These investigations will provide insights into its role in tumor development. Understanding this fusion's impact on tumor progression is critical. It can help clarify the molecular pathways involved in malignancy. Such knowledge may also aid in identifying potential therapeutic targets. Potential therapeutic targets in the TGF-β/SMAD signaling pathway for tumors should also be explored, focusing on key targets such as TGF-β ligands, receptors, and downstream signaling components. Studying more case reports will improve our understanding of the tumor's behavior, outcomes, and factors that influence prognosis. This will help make diagnoses more accurate and provide better treatments.

Conclusion

The EWSR1-SMAD3-positive fibroblastic tumor is an example of the critical role of molecular diagnostics. For the diagnostic accuracy understanding of clinicopathological and molecular features is mandatory. It can guide appropriate therapeutic decisions. As this emerging entity gains recognition, such insights are vital for advancing patient care.

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