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Case Report

Undifferentiated Pleomorphic Sarcoma with a Likely Nonfunctional *EWSR1::NF2* Fusion and Complex Genomic Background: A Case Report

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Abstract

Background: *EWSR1* fusions are recurrent genetic alterations in a wide spectrum of mesenchymal tumors and are often associated with specific clinicopathologic entities. However, the presence of an *EWSR1* rearrangement does not always indicate a functional or disease-defining fusion.

Case presentation: We report a case of undifferentiated pleomorphic sarcoma with high-grade morphologic features harboring an *EWSR1* rearrangement detected by fluorescence *in situ* hybridization. It was subsequently characterized by RNA sequencing as a likely nonfunctional fusion of *EWSR1* exon 1 and *NF2* intron 1. Histologically, the tumor was composed of pleomorphic spindle cells with brisk mitotic activity and lacked a specific line of differentiation. Immunohistochemically, the tumor showed diffuse cytoplasmic S100 positivity, with nuclear staining in a subset of tumor cells, while the overall immunophenotype did not support a specific line of differentiation. The *EWSR1::NF2* fusion was inferred to have a tail-to-tail configuration, and additional *KRAS* and *TP53* alterations were detected.

Conclusions: This case highlights that an *EWSR1* rearrangement detected by fluorescence *in situ* hybridization should be interpreted cautiously and does not necessarily represent a functional or disease-defining fusion. Comprehensive molecular evaluation is important for the accurate interpretation and classification of sarcomas with atypical *EWSR1* rearrangements.

Introduction

EWSR1 gene rearrangements are recurrent molecular alterations identified in a broad spectrum of mesenchymal neoplasms and are typically associated with specific clinicopathologic entities, including Ewing sarcoma,[1] clear cell sarcoma,[2] desmoplastic small round cell tumor,[3] extraskeletal myxoid chondrosarcoma,[4] and angiomatoid fibrous histiocytoma.[5] More recently, superficial neurocristic *EWSR1::FLI1* fusion tumor has also been recognized as a distinct *EWSR1*-rearranged neoplasm, further expanding the spectrum of tumors associated with *EWSR1* rearrangements.[6,7] In these tumors, *EWSR1* forms oncogenic fusion proteins with a variety of partner genes, serving as key drivers of tumorigenesis and providing important diagnostic implications.[8,9] However, with the increasing application of next-generation sequencing (NGS), noncanonical and potentially nonfunctional *EWSR1* rearrangements are increasingly recognized, and not all such events result in functional or disease-defining fusions. These findings raise important diagnostic challenges, as the presence of an *EWSR1* rearrangement alone may lead to misclassification as a fusion-driven sarcoma if not interpreted in the appropriate morphologic, immunophenotypic, and molecular context.

NF2 is a well-established tumor suppressor gene encoding Merlin, a key regulator of contact inhibition and Hippo signaling,[10] and is only rarely involved as a fusion partner in mesenchymal tumors. To date, *EWSR1::NF2* fusion has been rarely reported,[11] and its clinicopathologic significance remains to be fur-

Keywords: *EWSR1* rearrangement; *NF2*; Nonfunctional fusion; Undifferentiated pleomorphic sarcoma; Molecular pathology; RNA sequencing; Fluorescence *in situ* hybridization.
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ther characterized.

Here, we report an undifferentiated pleomorphic sarcoma with high-grade morphologic features demonstrating *EWSR1* rearrangement by fluorescence *in situ* hybridization (FISH), in which RNA sequencing identified an *EWSR1::NF2* fusion. Notably, the fusion is inferred to have a tail-to-tail configuration, which is unlikely to preserve an in-frame coding sequence and therefore is unlikely to generate a functional chimeric protein, although its biological consequences have not been experimentally validated. This case underscores the importance of integrating morphologic, immunophenotypic, and molecular findings when interpreting *EWSR1* rearrangements in sarcomas.

Case presentation

A 75-year-old man presented with a 4-month history of progressive pain and swelling in the proximal left thigh. Magnetic resonance imaging (MRI) performed at an outside hospital revealed a large soft tissue mass. A subsequent core needle biopsy suggested a spindle cell sarcoma, with further evaluation of the resection specimen recommended. The resected specimen measured 22 × 12 × 8 cm, with a solid gray-white cut surface and areas of necrosis. The tumor was completely resected with negative margins.

Histologically, the tumor was composed of atypical spindle to irregularly shaped cells arranged in sheets and short fascicles, with a focally prominent vascular network in the stroma (Fig. 1a and b). The tumor showed marked cytologic and nuclear pleomorphism, with moderate to abundant eosinophilic cytoplasm and prominent nucleoli in some cells. Mitotic figures were readily identified, including occasional atypical forms (Fig. 1c and d). Immunohistochemically, the tumor cells showed diffuse cytoplasmic positivity for S100, with nuclear staining in a subset of tumor cells (Fig. 2a), while SOX10 was negative (Fig. 2b). H3K27me3 expression was retained (Fig. 2c). The tumor cells showed diffuse positivity for EMA (Fig. 2e) and positivity for SATB2 (Fig. 2f), whereas pan-cytokeratin (Fig. 2d), CD99 (Fig. 2g), NKX2.2 (Fig. 2h), and MUC4 (Fig. 2i) were negative. The tumor cells were also negative for desmin (Fig. 2j), smooth muscle actin, myogenin (Fig. 2k), MyoD1, and CD34. HMB45, Melan-A, and STAT6 were negative (not shown). The Ki-67 labeling index was approximately 60% in hotspot areas (Fig. 2l). Despite the marked nuclear pleomorphism, the diffuse S100 expression in the absence of lineage-specific differentiation prompted further molecular evaluation for a possible EWSR1-rearranged sarcoma. FISH analysis demonstrated an *EWSR1* gene rearrangement using a break-apart probe (Fig. 3a). No *SS18* (formerly *SYT*) gene rearrangement was detected (Fig. 3b). Taken together, the histomorphology, immunophenotype, and molecular findings supported a diagnosis of undifferentiated pleomorphic sarcoma, with detection of an *EWSR1* rearrangement of uncertain significance.

To further characterize the molecular basis, both targeted DNA and RNA sequencing were performed. Targeted RNA sequencing identified an *EWSR1::NF2* fusion involving *EWSR1* exon 1 and *NF2* intron 1. The fusion was inferred to have a tail-to-tail configuration, as illustrated in Figure 3c. Based on these structural features, the fusion is unlikely to preserve an in-frame coding sequence. The potential functional consequences of this rearrangement remain unclear.

Targeted DNA sequencing using a soft tissue and bone tumor–related gene panel revealed three variants classified as Tier II in the molecular diagnostic report: *KRAS* p.G13D (variant allele frequency (VAF), 14.9%), *TP53* c.672+1G>T (VAF, 61.9%), and *SMARCA4* c.2959_2973+11delinsTCGACTTCCTTC (VAF, 3.4%). The *SMARCA4* variant was detected at a sequencing depth of 2,502×. No Tier I variants (variants with strong clinical significance) were identified. In addition, a Tier III variant of uncertain significance, *MYOD1* p.A266P (VAF, 33.3%), was detected. The tumor was microsatellite stable. No *MDM2* amplification was detected by targeted NGS.

Following surgical resection, the patient received adjuvant radiotherapy. MRI performed shortly after surgery demonstrated multiple osseous lesions in the left pelvis suspicious for metastatic disease. Follow-up MRI approximately 1 year later showed a decrease in the postoperative soft-tissue abnormality at the primary site, with no evidence of local recurrence, while the pelvic osseous lesions remained suspicious for metastatic disease. During follow-up, the patient also received anlotinib therapy. At the latest follow-up (approximately 1 year after surgery), the patient was alive and under follow-up. The clinical course of the patient, including diagnostic evaluation, treatment, and follow-up, is summarized in Figure 4.

Molecular analysis was performed on formalin-fixed paraffin-embedded tumor tissue. Targeted DNA sequencing was performed using a soft tissue and bone tumor-related gene panel based on NGS and PCR-based fragment analysis. The assay was performed on an Illumina platform (NextSeq500/NovaSeq6000) using the GRCh37/hg19 reference genome. The panel covered 52 genes associated with soft tissue and bone tumors and was designed to detect single nucleotide variants, small insertions/deletions, selected copy number alterations, microsatellite instability, and selected gene fusions. The tumor content was approximately 90%, with an average sequencing depth of 4,172.45×. Sequence variants were classified according to the tier-based system recommended by the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.[12]

Targeted RNA sequencing was performed using a fusion gene panel covering 110 genes associated with soft tissue and bone tumors on the Illumina platform (NextSeq500/NovaSeq6000). A total of 114.4 million effective reads were generated. The *EWSR1::NF2* fusion was identified with breakpoints involving *EWSR1* (NM_001163285, exon 1; chr22:29664338) and *NF2* (NM_181825, intron 1; chr22:30000331). The bioinformatic analysis showed 29 and 27 split reads at the EWSR1 and NF2 breakpoints, respectively.

FISH was performed using break-apart probes for *EWSR1* and *SS18*. For *EWSR1* and *SS18* rearrangement analysis, at least 100 tumor nuclei were evaluated, and a split-signal rate exceeding 15% was considered positive according to the laboratory criteria.

Discussion

EWSR1 rearrangements are among the most well-characterized molecular alterations in soft tissue tumors and are typically associated with oncogenic fusion proteins that define specific clinicopathologic entities.[13] In canonical settings, such as Ewing sarcoma or clear cell sarcoma, these fusion proteins act as key drivers

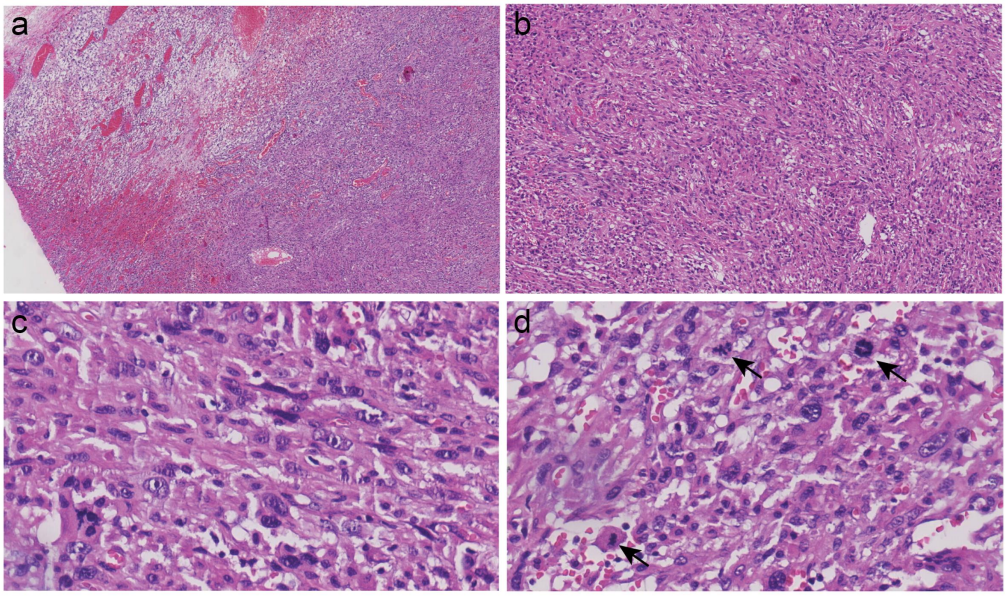

Fig. 1. Representative hematoxylin and eosin staining. (a–b) Low-power views (×40 and ×100, respectively) showing a cellular sarcoma composed of atypical spindle to irregularly shaped cells, with a focally prominent vascular network in the stroma. (c–d) High-power views (×400) demonstrating marked cytologic and nuclear pleomorphism, prominent nucleoli, and mitotic activity; black arrowheads indicate mitotic figures.

of tumorigenesis and provide strong diagnostic and biological relevance.

However, accumulating evidence indicates that not all *EWSR1* rearrangements correspond to functional oncogenic fusions. Although *EWSR1* break-apart FISH is a valuable tool for detecting rearrangements involving the *EWSR1* locus, the presence of a rearrangement alone does not necessarily indicate the existence of a pathogenic fusion transcript. Discordant cases have been reported in which an EWSR1 rearrangement was detected by FISH, but no corresponding fusion transcript was identified by RNA sequencing, underscoring the need for cautious interpretation of break-apart FISH results.[14] Furthermore, atypical EWSR1 rearrangements may represent complex genomic events rather than disease-defining oncogenic fusions. Such rearrangements may not result in functional fusion transcripts. A functional *EWSR1* fusion protein generally requires preservation of critical functional domains and an appropriate in-frame configuration, which may be disrupted in atypical rearrangements.

In the present case, FISH demonstrated an *EWSR1* rearrangement, which could have suggested a diagnosis within the spectrum of *EWSR1*-rearranged sarcomas. However, the morphologic and immunophenotypic findings were not consistent with any well-defined *EWSR1*-associated entity. RNA sequencing further identified an *EWSR1::NF2* fusion involving *EWSR1* exon 1 and *NF2* intron 1, which was inferred to have a tail-to-tail configuration, suggesting that the two genes are arranged in opposite transcriptional orientations with their 3′ ends facing each other. This fusion architecture is unlikely to preserve a canonical in-frame transcript and therefore is unlikely to encode a canonical functional chimeric protein. Notably, *NF2* is a tumor suppressor gene and has only rarely been reported as a fusion partner of *EWSR1*, with its biological significance remaining uncertain.[11] A recently reported rhabdomyosarcoma case harboring an *EWSR1::NF2* fusion involved *EWSR1* exon 9 and *NF2* exon 7, resulting in an in-frame fusion with retained protein domains, suggesting a potential functional fusion product.[11] In contrast, the *EWSR1::NF2* rearrangement identified in our case was inferred to have a tail-to-tail configuration involving *EWSR1* exon 1 and *NF2* intron 1, which is unlikely to preserve a canonical in-frame coding sequence or generate a functional chimeric protein. Although this configuration argues against a canonical oncogenic fusion mechanism, the possibility that this rearrangement may influence *NF2* function or other genomic processes cannot be excluded.

Importantly, additional genomic alterations, including *KRAS* p.G13D and *TP53* mutations, were detected. Although activating *KRAS* mutations have occasionally been reported in undifferentiated pleomorphic sarcoma, they appear to be uncommon.[15] A previous case described an undifferentiated pleomorphic sarcoma harboring concurrent *KRAS* G12D and *PIK3CA* mutations, whereas a larger cohort study identified only a single *KRAS* mutation among 33 molecularly analyzed undifferentiated pleomorphic sarcomas.[15,16] The *KRAS* p.G13D identified in our case is a well-established activating hotspot mutation in epithelial malignancies; however, its biological significance in undifferentiated pleomorphic sarcoma remains uncertain. The difference in VAF between *TP53* (61.9%) and *KRAS* (14.9%) may reflect differences in clonal representation; however, in the absence of matched normal tissue and allele-specific copy-number analysis, loss of heterozygosity and clonal architecture cannot be definitively determined. The low-VAF *SMARCA4* alteration (3.4%) should also be interpreted cautiously. Although the biological significance of these alterations cannot be determined from a single case, their coexistence may suggest that the tumor is not driven by a single recurrent fusion event. This finding further supports the need for cautious interpretation of *EWSR1* rearrangements, as the presence of additional genomic alterations may indicate a more

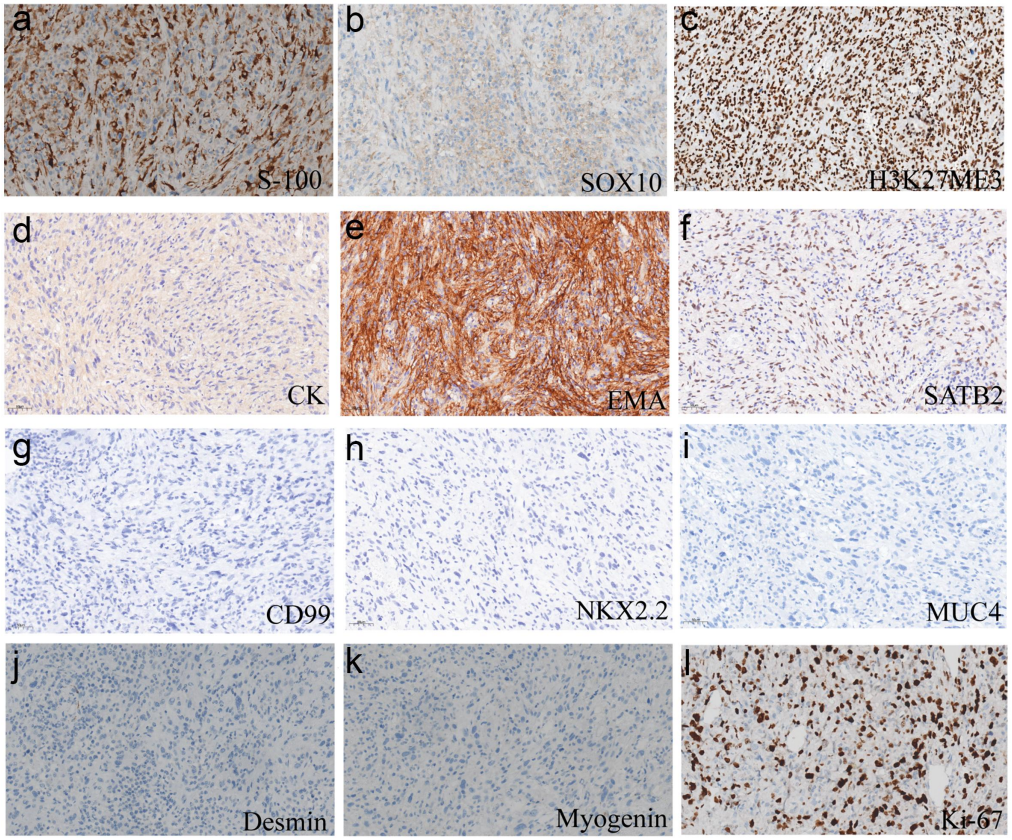

Fig. 2. Immunohistochemical staining of the tumor. (a) Diffuse cytoplasmic positivity for S100 with nuclear staining in a subset of tumor cells (×200). (b) Negative staining for SOX10 (×200). (c) Retained nuclear expression of H3K27me3 (×200). (d) Negative staining for pan-cytokeratin (pan-CK) (×200). (e) Diffuse positivity for EMA (×200). (f) Positive staining for SATB2 (×200). (g) Negative staining for CD99 (×200). (h) Negative staining for NKX2.2 (×200). (i) Negative staining for MUC4 (×200). (j) Negative staining for desmin (×200). (k) Negative staining for myogenin (×200). (l) High proliferative activity with a Ki-67 labeling index of approximately 60% (×200).

complex molecular landscape.

From a diagnostic perspective, *EWSR1* rearrangement alone should be interpreted in the context of morphologic, immunophenotypic, and transcript-level molecular findings. The differential diagnosis of this tumor included several spindle cell neoplasms, particularly S100-positive entities such as malignant peripheral nerve sheath tumor, spindle cell melanoma, clear cell sarcoma, and the recently described superficial neurocristic *EWSR1::FLI1* fusion tumor,[6,7] as well as other *EWSR1*-rearranged or morphologically overlapping tumors, including dedifferentiated liposarcoma and Ewing/Ewing-like sarcoma. Malignant peripheral nerve sheath tumor was considered; however, the immunophenotype, including negative SOX10 expression and retained H3K27me3 expression, did not support this diagnosis. Dedifferentiated liposarcoma was considered unlikely given the absence of a well-differentiated liposarcoma component and the absence of *MDM2* amplification by targeted NGS. Melanocytic tumors, including spindle cell melanoma and clear cell sarcoma, were not favored due to the absence of melanocytic differentiation markers (HMB45 and Melan-A). Ewing/Ewing-like sarcoma was also considered because of the *EWSR1* rearrangement; however, the marked nuclear pleomorphism, spindle cell morphology, and lack of a canonical *EWSR1::ETS* family fusion were not supportive of this diagnosis. The recently described superficial neurocristic *EWSR1::FLI1* fusion tumor was considered due to its diffuse S100 expression and *EWSR1* rearrangement but was unlikely given the absence of SOX10 expression, marked cytologic pleomorphism, and the lack of the characteristic *EWSR1::FLI1* fusion. Myoepithelial tumor was considered because of the S100 positivity and *EWSR1* rearrangement; however, the overall morphology, immunophenotype, and molecular findings were not consistent with this diagnosis. Synovial sarcoma was excluded by the absence of *SS18* rearrangement and characteristic morphologic features.

Collectively, the morphologic, immunohistochemical, and molecular findings supported the diagnosis of undifferentiated pleomorphic sarcoma. These findings emphasize the need for careful interpretation of *EWSR1* rearrangements in the appropriate morphologic and molecular context.

Limitations

This report describes a single case, and additional cases are required to determine the frequency and clinical significance of *EWSR1::NF2* fusion and other atypical *EWSR1* rearrangements.

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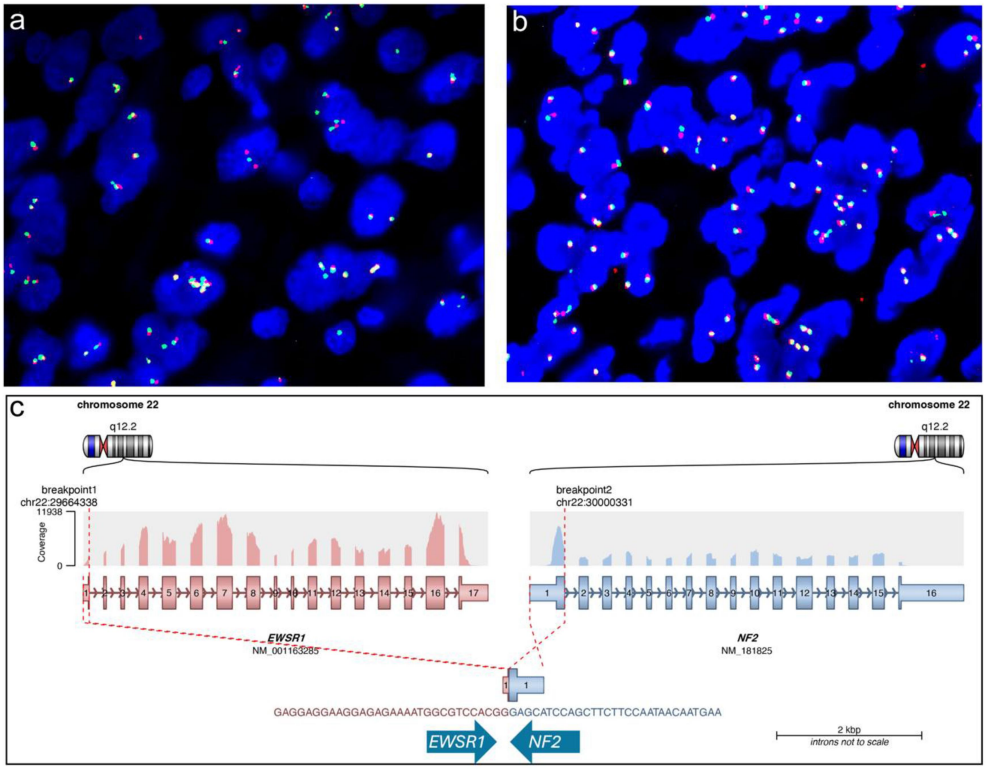

Fig. 3. Molecular analyses of the tumor. (a) *EWSR1* break-apart probe showing split signals indicating *EWSR1* gene rearrangement (×1000). (b) *SS18* break-apart probe showing intact fused signals, indicating no *SS18* gene rearrangement (×1000). (c) Schematic representation of the *EWSR1::NF2* fusion identified by targeted RNA sequencing, illustrating the inferred tail-to-tail configuration, in which the two genes are arranged in opposite transcriptional orientations with their 3′ ends facing each other. The schematic was derived from the targeted RNA sequencing report provided by Guangzhou KingMed Diagnostics and reproduced with permission.

Although the predicted tail-to-tail configuration suggests that the *EWSR1*::*NF2* fusion is unlikely to generate a canonical functional chimeric protein, functional studies were not performed, and the potential impact of this rearrangement on *NF2* function remains uncertain. In addition, the limited follow-up duration precludes a comprehensive assessment of the long-term clinical behavior of this tumor.

Conclusions

We report an undifferentiated pleomorphic sarcoma harboring an *EWSR1* rearrangement with an *EWSR1*::*NF2* fusion that is unlikely to encode a functional chimeric protein. This case highlights that an *EWSR1* rearrangement detected by FISH should not be interpreted as definitive evidence of a functional or disease-defining fusion. Integrated morphologic, immunohistochemical, and molecular evaluation is important for the accurate classification of tumors with atypical *EWSR1* rearrangements.

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Conflict of interest

Dr. Anjia Han is an editorial board member of *Journal of Clinical and Translational Pathology*. The authors declare no other conflicts of interest.

Author contributions

Study design, data interpretation, manuscript preparation (HW, JL), study supervision, pathological diagnosis, critical revision of the manuscript (AH), performance of immunohistochemical staining, and assistance with data interpretation (FZ, YD). All authors read and approved the final manuscript.

Ethical statement

Ethical approval for this study was granted by the Institutional Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University, and the requirement for informed consent was waived by the ethics committee (Approval No. [2025]599). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024).

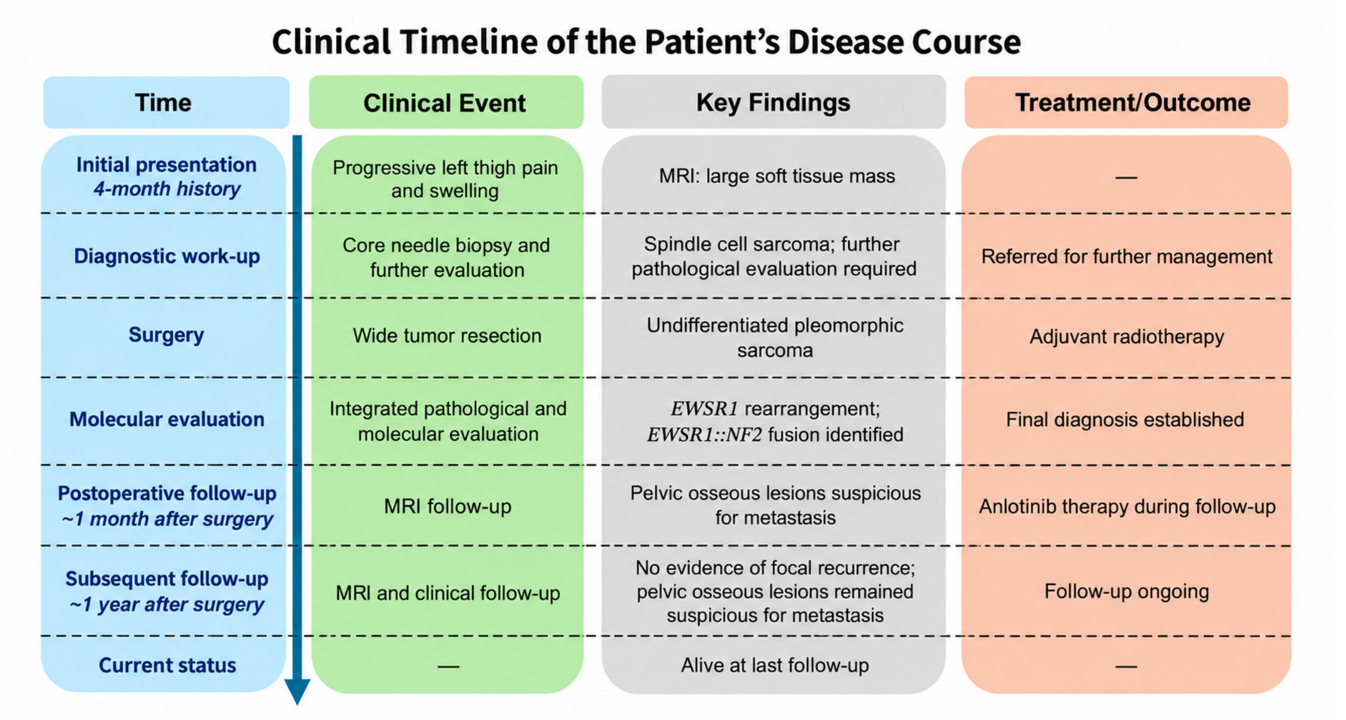

Fig. 4. Clinical timeline of the patient's disease course. The timeline summarizes the major clinical events, diagnostic evaluation, treatment interventions, and follow-up information from initial presentation to the latest follow-up. MRI, magnetic resonance imaging.

Data sharing statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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