CANCER DIAGNOSIS & PROGNOSIS *5*: 620-624 (2025)
doi: 10.21873/cdp.10477

Definitive Diagnosis of Angiomatoid Fibrous Histiocytoma Using Dual DNA/RNA Genomic Profiling

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Abstract

Background/Aim: Angiomatoid fibrous histiocytoma (AFH) is a rare soft-tissue tumor that typically occurs in young individuals and often mimics hematomas or sarcomas. Its diagnosis is difficult due to nonspecific histological features, and identification of gene fusions such as EWSR1–CREB1 is crucial. We report a case definitively diagnosed using GenMineTOP, a dual DNA/RNA genomic profiling panel.

Case Report: A 61-year-old woman presented with acute onset of pain and swelling in the right popliteal fossa, initially diagnosed as a hematoma. MRI revealed a 10-cm intramuscular mass with heterogeneous signal intensity and fluid-fluid levels. Needle biopsy showed no tumor cells. Despite transient improvement, the mass persisted and anemia worsened, prompting surgical excision. The tumor was resected with marginal margins, and histology revealed large atypical cells with unclear differentiation. Postoperative radiotherapy (60 Gy in 30 fractions) was administered under suspicion of sarcoma. GenMineTOP testing identified an EWSR1–CREB1 fusion gene. Reevaluation confirmed AFH with characteristic lymphoid cuffs and CD68 positivity. One year postoperatively, the patient remains free of recurrence and metastasis.

Conclusion: This case underscores the diagnostic challenges of AFH, particularly in older patients with deep-seated lesions mimicking hematomas. Dual DNA/RNA genomic profiling enabled definitive diagnosis and demonstrated its clinical utility in evaluating soft-tissue tumors with ambiguous histopathological features.

Keywords: Angiomatoid fibrous histiocytoma, soft-tissue tumor, genomic profiling, EWSR1-CREB1, case report.

Introduction

Angiomatoid fibrous histiocytoma (AFH) is a rare soft-tissue tumor of intermediate malignancy, first described by Enzinger in 1979 (1). Although most commonly found in the extremities of children and young adults, cases involving deep soft tissues and older individuals have also been reported (2, 3). Clinically, AFH typically presents as a slow-growing, painless mass, and may occasionally be accompanied by systemic symptoms such as anemia, fever, or spontaneous regression (4). Magnetic resonance imaging (MRI) often reveals cystic components and

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Received June 22, 2025 | Revised July 5, 2025 | Accepted July 11, 2025

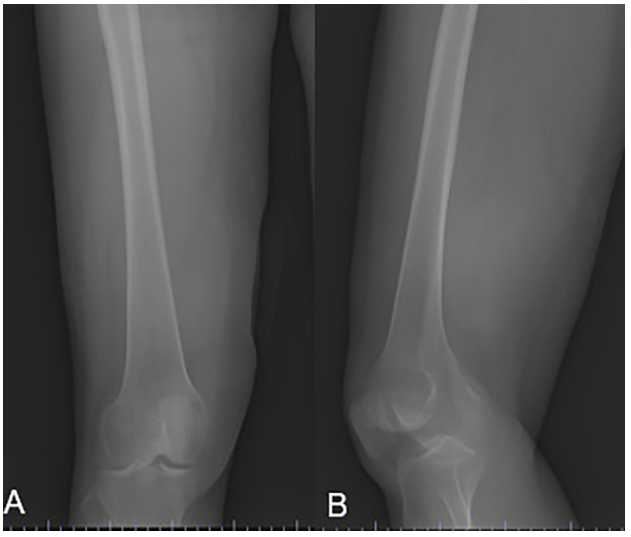

Figure 1. *Anteroposterior (A) and mediolateral (B) radiograph of the distal right thigh showing a soft-tissue mass posterior to the femur.*

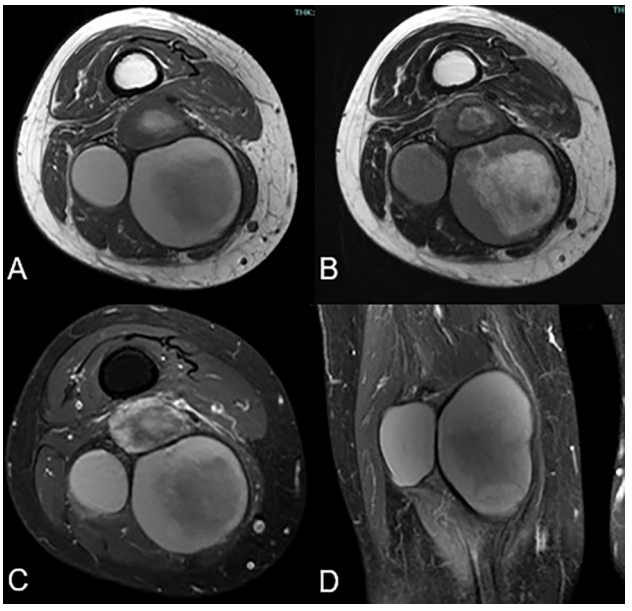

Figure 2. *MRI showing T1- weighted (A) ,T2-weighted (B), and enhanced T1-weighted (C,D) images with heterogeneous signal and hemorrhagic features. MRI: Magnetic resonance imaging.*

intratumoral hemorrhage, which can mimic hematomas or hemorrhagic sarcomas (5).

Histologically, AFH exhibits spindle to oval cells with mild atypia, pseudovascular hemorrhagic spaces, and fibrous pseudocapsules with lymphoid cuffs (6). Immunohistochemistry is often inconclusive, but fusion genes such as EWSR1–CREB1, EWSR1–ATF1, and FUS–ATF1 are characteristic (7). In Japan, GenMineTOP, a dual DNA/RNA profiling platform, became clinically available under insurance in 2023, enhancing diagnostic capabilities in rare soft-tissue tumors (8). We report a case of AFH in a 61-year-old woman diagnosed *via* GenMineTOP.

Case Report

A 61-year-old woman presented with acute pain and swelling in the right popliteal fossa. Initial clinical assessment suggested a subcutaneous hematoma. Physical examination revealed an elastic-soft, tender mass accompanied by ecchymosis. Radiographs of the right thigh demonstrated enhancement of soft tissue shadows (Figure 1). Magnetic resonance imaging (MRI) showed a 10-cm intramuscular lesion with heterogeneous T2 signal hyperintensity, intratumoral hemorrhage, and a surrounding fibrous capsule (Figure 2). Laboratory testing revealed a hemoglobin level of 9.7 g/dl. A core needle biopsy yielded only hemorrhagic material.

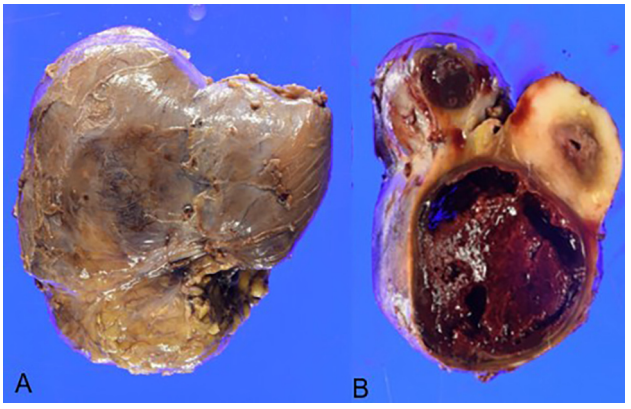

Figure 3. *Gross surgical specimen (A) and their sections (B) with fibrous capsule and hemorrhage.*

Although there was transient symptomatic improvement, the patient's anemia persisted, and the mass remained unchanged in size. Surgical excision was subsequently performed with marginal margins. Gross examination revealed a well-encapsulated tumor with prominent

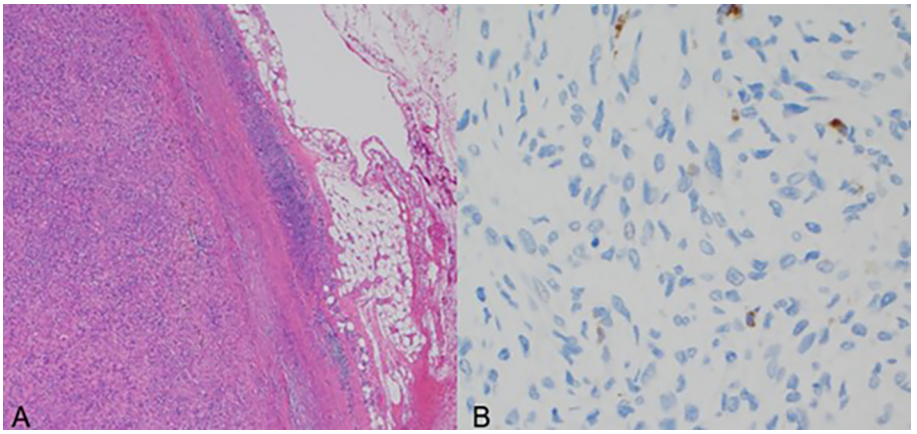

Figure 4. *Histopathology showing atypical spindle cells, lymphoid cuff (H&E) (A), and CD68 positivity (B). H&E: Hematoxylin-Eosin.*

Table I. *Summary of angiomatoid fibrous histiocytoma cases diagnosed via genomic profiling.*

Study (Ref)	Age/Sex	Tumor site	Fusion gene	Diagnostic method	Diagnosis timing	Treatment	Remarks
Argani P *et al.*, 2020 (12)	Various	Mesothelial-lined cavities (*e.g.*, pleura, peritoneum)	EWSR1/FUS–CREB1/CREM	FISH + RNA sequencing	Primary diagnosis based on fusion status	Surgical resection ± systemic therapy	Defined a new malignant epithelioid neoplasm subtype with FET–CREB fusions
Kobayashi H *et al.*, 2021 (13)	54/M	Intraosseous scapula	EWSR1–CREB1	RNA-seq (Archer FusionPlex Sarcoma) from FFPE	Postoperative fusion detection	Surgical resection	Fusion aligned with histopathology
Feng D *et al.*, 2024 (14)	34/M	Lung + 4th rib, metastatic	EWSR1–CREB1	FISH + Illumina RNA-seq	Preliminary FISH, confirmed by RNA-seq	Systemic chemotherapy	Transcript details defined

intratumoral hemorrhage (Figure 3). Histologically, large atypical cells with undetermined differentiation were observed. Given the concern for a high-grade sarcoma, postoperative radiotherapy (60 Gy in 30 fractions) was administered.

GenMineTOP testing was subsequently performed on formalin-fixed paraffin-embedded tissue, detecting an EWSR1–CREB1 fusion gene. Upon reevaluation, the tumor showed lymphoid cuffs and CD68-positive histiocytoid cells (Figure 4), confirming AFH. At one-year follow-up, the patient remains recurrence- and metastasis-free.

Ethics statement. Written informed consent was obtained from the patient for publication of this case report and accompanying images. This study was conducted in accordance with institutional ethical guidelines.

Discussion

AFH represents approximately 0.3% of all soft-tissue tumors and generally exhibits indolent clinical behavior (9). While it primarily affects children and young adults, it can also present in middle-aged individuals and deep tissue locations, posing diagnostic challenges (2, 3, 10). In the present case, the clinical and imaging findings mimicked a hematoma or hemorrhagic sarcoma, and the initial biopsy failed to reveal tumor cells.

Histopathological evaluation alone is often inconclusive, making molecular confirmation through fusion gene detection essential (7). Among these, the EWSR1–CREB1 fusion is the most frequently encountered in AFH (11). In Japan, cancer genome profiling (CGP) has been covered by the national health insurance system since 2019. Among available platforms, GenMineTOP, developed domestically, is currently the only CGP test approved for insurance reimbursement that performs simultaneous DNA and RNA co-analysis, as of 2023. It enables the analysis of DNA mutations in 737 genes and RNA fusions/expression in 455 genes from a single sample and reduces false positives and unknown mutations through tumor-normal pair analysis (8).

Table I summarizes previously reported cases of AFH diagnosed through RNA sequencing or other genomic panels (12–14). In diagnostically challenging cases with ambiguous histology, genomic profiling plays a pivotal role. Wide surgical excision is typically recommended, as recurrence and metastasis have been observed in incompletely resected or histologically atypical cases (15).

Conclusion

AFH is a rare, often underdiagnosed tumor due to non-specific clinical and radiological findings. Our case demonstrates the role of genomic profiling in resolving diagnostic uncertainty and guiding management. Dual DNA/RNA profiling should be considered in atypical soft-tissue tumors with ambiguous pathology.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conceptualization, N.T.; Investigation, N.T.; Writing – Original Draft, N.T.; Writing – Review and Editing, N.T., N.O., R.N., H.Y., K.K., H.T.

Acknowledgements

We thank the departments of orthopedic surgery and pathology at Osaka Metropolitan University for their support and diagnostic input.

Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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