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"THE DISGUISED STRANGER: RARE ARM TUMOUR REVEALED AS ANGIOMATOID FIBROUS HISTIOCYTOMA"

Pathology

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ABSTRACT

Angiomatoid fibrous histiocytoma is an uncommon soft tissue tumour characterized by an intermediate risk of malignancy, usually occurring in the subcutis. It exhibits a nodular and syncytial growth pattern of neoplastic cells that range from epithelioid to ovoid, along with hemorrhagic and pseudovascular spaces bordered by lymphoid follicles. We report a case of a 12-year-old female with a gradually enlarging, painless swelling on the right arm, treated by surgical excision. A brief review of the literature is included, highlighting the biological and genetic features, as well as the differential diagnosis of AFH.

KEYWORDS

Angiomatoid fibrous histiocytoma, Desmin, syncytium, Fluorescence in situ hybridisation, hemangioma

INTRODUCTION

Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue neoplasm first described by Enzinger in 1979 as angiomatoid malignant fibrous histiocytoma [1]. Subsequent studies clarified that AFH exhibits intermediate biological behavior rather than true malignancy [2]. In the 2020 WHO classification, AFH is categorized within the group of "tumours of uncertain differentiation" [3]. It primarily arises in the superficial soft tissues of the extremities, most often in children and young adults [1]. Histologically, it features epithelioid, ovoid, and spindle cells arranged in nodular and syncytial patterns, often with blood-filled cystic spaces and dense lymphoplasmacytic infiltrates. AFH is associated with distinctive gene fusions, most commonly EWSR1-CREB1 and EWSR1-ATF1, with FUS-ATF1 occurring less frequently [3]. Here, we report a case of AFH, highlighting its varied morphology, rarity, and the absence of a specific immunoprofile, which complicates diagnosis.

Case Report

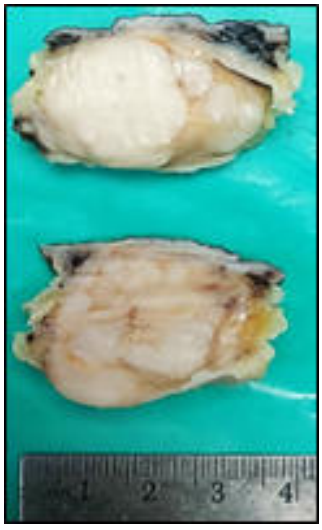

Figure 1: The wide local excision specimen reveals a well-defined subcutaneous lesion measuring 3.9 x 3.5 x 3 cm. The cut surface appears grey-white, firm, and lobulated, with no signs of cystic change, haemorrhage, or necrosis.

A 12-year-old girl presented with a gradually enlarging, painless swelling in the mid-right arm at the level of the brachialis. On examination, the lesion was soft, fixed to the deeper tissues, and not associated with the overlying skin. MRI of the right arm revealed a lobulated lesion with altered signal intensity, measuring 3.9 x 3.7 x 3.5 cm, located in the subcutaneous plane along the medial aspect, approximately 5 cm proximal to the elbow joint. The humerus, elbow joint, neurovascular bundles, and brachialis muscle appeared intact, with no evidence of infiltration, suggesting a mesenchymal neoplasm. The patient underwent a wide local excision. The specimen, received in 10% neutral buffered formalin, measured 4.5 x 4 x 3.8 cm, along with an overlying ellipse of skin measuring 4 x 4 cm, which was grossly unremarkable. Serial sectioning revealed a well-circumscribed subcutaneous lesion measuring 3.9 x 3.5 x 3 cm. The cut surface was firm, grey-white, and lobulated, without evidence of cystic change, haemorrhage, or necrosis [Figure 1].

Microscopically, the tumour was multinodular. The nodules consisted of epithelioid to oval cells arranged in syncytial and fascicular patterns. The tumour cells had round-to-oval nuclei with inconspicuous nucleoli and eosinophilic to clear cytoplasm. Scattered lymphoplasmacytic infiltrates were present within the lesion, along with areas of hyalinisation. The tumour was surrounded peripherally by lymphoid aggregates. Mitotic activity was sparse (0–1/10 HPF), and no necrosis was observed [Figure 2].

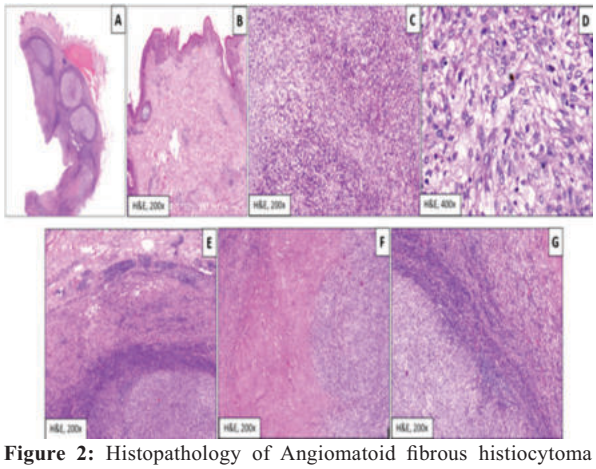

Figure 2: Histopathology of Angiomatoid fibrous histiocytoma

showing a well-circumscribed tumour in the subcutaneous plane with multiple nodules (A, H&E). The overlying skin appears unremarkable (B, H&E, 200x). The nodules consist of epithelioid to oval cells arranged in a syncytial and fascicular pattern (C, H&E x400). The cells have round to oval nuclei with inconspicuous nucleoli and eosinophilic to clear cytoplasm (D, H&E x400). Areas of hyalinisation were also observed (F, H&E x400). The lesion is peripherally surrounded by lymphoid aggregates (E, G, H&E x400).

Based on these features, the differential diagnoses included deep fibrous histiocytoma, angiomatoid fibrous histiocytoma, and follicular dendritic cell sarcoma. Immunohistochemistry showed positivity for Desmin, CD99, and CD68, while SMA, CD34, CD21, CD23, and EMA was negative. Additional markers, including CD1a, ALK, MyoD1, and β-catenin, were also negative. The Ki-67 proliferation index was low, at 3% (Figure 3).

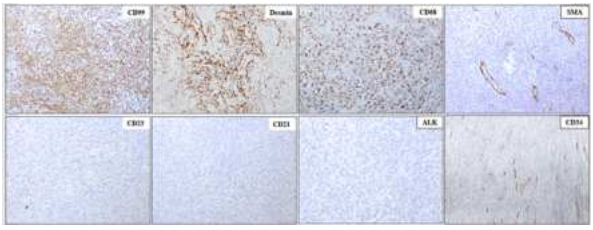

Figure 3: Immunohistochemistry showed positivity for CD99, Desmin, and CD68. SMA, CD23, CD21, ALK, and CD34 were negative.

Fluorescence in situ hybridisation (FISH) analysis for EWSR1 rearrangement revealed break-apart signals in 82% of tumour cells (Figure 4), confirming the diagnosis of angiomatoid fibrous histiocytoma (AFH).

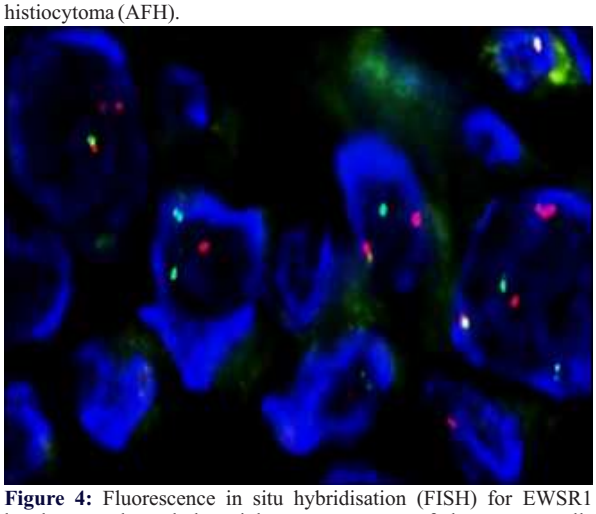

Figure 4: Fluorescence in situ hybridisation (FISH) for EWSR1 break-apart showed that eighty-two per cent of the tumour cells demonstrated EWSR1 rearrangement.

The patient is currently on follow-up and remains well.

DISCUSSION:

Angiomatoid fibrous histiocytoma (AFH) accounts for about 0.3% of all soft tissue tumours. In the current WHO classification, it is regarded as a mesenchymal neoplasm of uncertain differentiation with intermediate malignant potential [3, 4]. Clinically, AFH frequently presents as a superficial subcutaneous mass, often mistaken for a lymph node or benign cystic lesion [5]. It typically arises in the extremities, followed by the trunk, and is not linked to trauma or systemic symptoms [6–10]. AFH can occur at any age—from infancy to late adulthood—but peaks in the first three decades, with a higher incidence among children and young adults [2, 11–13]. Although previously misclassified as other fibroblastic soft tissue tumours [14], recognition of its distinctive morphology and EWSR1 gene rearrangements allows for accurate diagnosis. Rare cases have been reported in the breast [15], lung [16], and intracranial sites [17], sometimes presenting with paraneoplastic bleeding disorders [18]. Importantly, all reported cases, including those at unusual locations, consistently demonstrate EWSR1 fusion. Patients with angiomatoid fibrous histiocytoma (AFH) typically present with a slow-growing, superficial, painless soft tissue mass, which may resemble a hematoma or hemangioma clinically [1, 8, 9]. These tumours are usually small, firm, and either nodular or cystic, ranging from 0.7 to 12 cm in size, with a median diameter of approximately 2 cm [1, 2]. On gross examination, the cut surface often reveals multilocular hemorrhagic areas resembling a hematoma, with colours ranging from yellowish-tan to white, fleshy tissue [1, 2, 14]. The key histological features of angiomatoid fibrous histiocytoma (AFH) include a fibrous pseudocapsule, nodular proliferation of spindled to ovoid fibrohistiocytic cells, pseudoangiomatoid spaces, and a prominent peripheral lymphoplasmacytic infiltrate [9, 11, 14]. Additionally, several atypical histopathological variants have been reported, such as schwannoma-like areas, small round cell morphology resembling Ewing sarcoma, rhabdomyoblast-like cells, nuclear grooves, apparent cell change, as well as myxoid, edematous, and sclerotic alterations [9, 10, 19]. Immunohistochemically, the neoplastic spindled to epithelioid cells show desmin positivity in about 50% of cases, while EMA, CD99, and CD68 demonstrate variable expression in nearly half of the tumours [3]. Molecular testing can further confirm the diagnosis, with the most common genetic alteration being the translocation t(2;22)(q33;q12), which produces the EWSR1–CREB1 fusion, identified in more than 90% of cases. Less frequently, the translocation t(12;22)(q12;q12), resulting in an EWSR1–ATF1 fusion, is observed [3, 20]. A series from Mumbai reported the EWSR1–CREB1 fusion in one of five patients, representing one of the few documented series from India [11]. Given the significant variability in histomorphology and immunoprofiles, testing for EWSR1 rearrangements is essential for confirming the diagnosis. Clinically, AFH generally follows an indolent course, with local recurrence rates of 15–20% and distant metastasis occurring in only 1–3% of cases [3]. Table 1 provides a complete list of AFH cases in younger patients (<18 years old) reported in the literature.

Table 1: List of AFH Cases In Younger Patients (<18 years old) Reported In The Literature.

Ref	Author, Year	Age/Sex	Site	IHC profile		Molecular test	Follow-up
				Positive	Negative		
	Present case	*11/F*	*Right arm*	*Desmin, CD99, CD68*	*SMA, CD34, CD21, CD23, EMA, CD1a, ALK, MyoD1, β-catenin*	*FISH analysis for EWSR1 rearrangement revealed break-apart signals*	*No recurrence*
22	Pasricha S et al., 2022	6/F	Right LL	Desmin, EMA, TLE-1, Vimentin, CD99	CK, SMA, S-100, CD31, h-caldesmon, myogenin, Myo D1.	Not done	No recurrence
21	Bauer et al., 2012	11/F	Right thigh	Desmin and EMA	Not mentioned	Not done	No recurrence
23	Mangham et al., 2010	11/M	Right upper arm	Desmin, EMA, CK	CD34, CD31, CD45, S100, SMA, HMB45, MyoD1, Myogenin	EWSR1-ATF1 fusion	No recurrence
24	Cernik et al., 2009	6/M	Arm	Desmin, EMA and CD68.	Myogenin, MYOD1, and endothelial markers.	Not Done	----

25	Weinreb et al., 2008	8/M	Scalp	CD99, Factor 3a, Desmin, and SMA	S100, pankeratin	EWSR1 translocation on 22q12	No recurrence
26	Martelli et al., 2008	7/F	Right Knee	Desmin	S100, CD68, SMA		No recurrence
27	Hallor et al., 2007	11/M	Paravertebral	-----	-----	EWSR1-ATF1 fusion genes	No recurrence
		10/M	Right clavicular region	-----	-----	EWSR1-ATF1 fusion genes	No recurrence
28	Pratibha and Ahmed, 2006	13/F	Left lower jaw	CD68	Desmin and Keratin		
29	Hallor et al., 2005	9/M	Right Elbow	CD68, vimentin	S100, CD1a, cytokeratin, EMA, CD21, CD31, CD34, HMB45, and Melan A	EWSR1-ATF1 fusion gene	No recurrence

CONCLUSIONS

Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue tumour with intermediate malignant potential, most often developing in the superficial extremities of children and young adults. It generally has a favourable prognosis but can recur locally, highlighting the importance of accurate diagnosis. The tumour exhibits bland cytology with various morphologic patterns, which can make identification challenging. Molecular techniques, especially fluorescence in situ hybridisation (FISH), are crucial for distinguishing AFH from similar histologic entities and ensuring diagnostic accuracy.

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