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CASE REPORT

An unusual histopathologic feature of angiomatoid fibrous histiocytoma – A case report and molecular study

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ABSTRACT

Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue tumor with intermediate malignant potential. It predominantly affects children and young adults and is most often located in the extremities. The atypical pattern of AFH may create significant diagnostic difficulty. We present a case of AFH diagnosed via molecular confirmation by fluorescence in situ hybridization (FISH) and also review cases of AFH with atypical histologic presentations in Taiwan. We present this case to remind clinicians that identification of gene fusions by molecular testing is a valuable diagnostic tool for AFHs, especially in cases with atypical histopathological presentations.

Introduction

Angiomatoid fibrous histiocytoma (AFH), also known as angiomatoid malignant fibrous histiocytoma, is a rare soft tissue tumor of intermediate malignant potential.[1] It predominantly affects children and young adults and develops most frequently on the extremities, followed by the trunk, head and neck.[2] Its diagnosis poses a challenge because an AFH may not display all of the classic histological features. Identification of gene fusions by molecular testing can be a valuable diagnostic tool for AFHs, especially in cases with atypical clinicopathological presentations.[3] We present here a case of AFH lacking the typical clinical pattern, and we describe the molecular confirmation of AFH by fluorescence in situ hybridization (FISH).

Case report

A 30-year-old female presented with a 1.5 × 0.8 × 0.5 cm, asymptomatic, slow-growing skin tumor on her right wrist that had been present for 15 years. There was no traumatic history. The tumor was excised due to suspicions of osteochondroma and keloid. Its histologic appearance showed hyperkeratosis of the epidermis, as well as a dermal lesion with an ill-defined border. The lesion was composed of ovoid and short spindle tumor cells arranged in a multinodular pattern, as well as scattered multinucleated giant cells (Fig. 1A and B). No cellular pleomorphism or mitotic figures were evident, but fibrosis and focal myxoid changes were noted. Immunohistochemically, the tumor cells were pan cytokeratin (−), p63 (−), S-100 protein (−), desmin (+, focal), SMA (+, focal), CD34 (−), CD68 (+), and GFAP (−) (Fig. 1C and D). Accordingly, despite the absence of the usual features, such as peritumoral lymphoid cuffing, AFH was strongly suspected. FISH was used to look for an EWS gene and revealed diagnostic break-apart signals (Fig. 1E and F). The histological, immunohistochemical staining, and molecular findings thus supported a diagnosis of AFH without lymphoid cuffing. No evidence of recurrence was observed after excision during 4 years of follow-up.

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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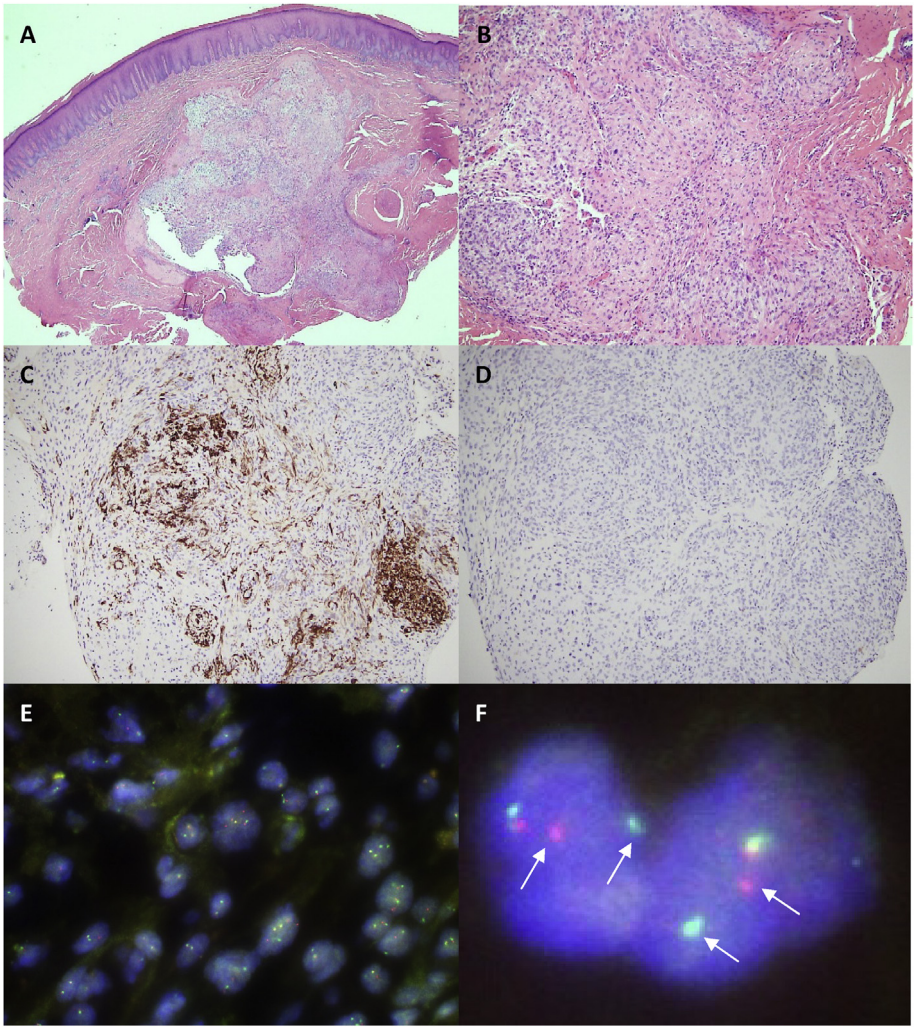

Fig. 1 (A) and (B) A dermal lesion with an ill-defined border and composed of ovoid to short spindle tumor cells arranged in cannonball-like pattern, with occasional multinucleated giant cells. The tumor cells showed positive immunohistochemistry for desmin (C) and negative immunohistochemistry for S-100 protein (D). (H&E section, original magnification: 40× (A) and 100× (B); immunohistochemical stains, original magnification: 100×). (E) and (F)The *EWS* fluorescence in situ hybridization (FISH) showed break apart -signals in the tumor cells, indicating *EWS* gene rearrangement (white arrow: break-apart signals).

Discussion

AFH, a rare soft tissue tumor, was first described by Enzinger in 1979. Most AFHs occur during an individual's first two decades of life and often present as slow-growing, superficial nodular masses.[3,4] AFH most commonly occurs in the deep dermis or subcutaneous tissues of the extremities, followed by the trunk, head and neck. It is also rarely found in visceral organs such as the lung, brain, and mediastinum.[5–7]

The histology of typical AFHs is characterized by multinodular proliferation of oval histiocytoid to spindle cells with syncytial growth; these form sheets, whorls, or vague bundles and are accompanied by three features: central pseudoangiomatous spaces, a thick fibrous pseudocapsule, and pericapsular lymphoplasmacytic cuffing of varying proportions.[8,9] Typically, mitotic figures are not prominent.[6,10] Immunohistochemistry results show variable positivity for epithelial membrane antigen (EMA), desmin, CD68, and CD99, whereas the S100 protein and cytokeratin are negative.[1,7] AFH is also associated with three characteristic translocations, which generate corresponding fusion genes; the most prevalent is *EWSR1- CREB1*, derived from t(2;22)(q33;q12), followed by *EWSR1-ATF1,* from t(12;22)(q13;q12). The least common is *FUS-ATF1* from t(12;16)(q13; p11). *EWSR1-CREB1*, the most commonly noted gene fusion, has been reported in more than 90% of AFHs.[3,6,10,11]

Furthermore, AFH sometimes has variant histological patterns. Unusual morphologic features have included sclerosis, nuclear grooving, clear cell change, rhabdomyoblast-like cells, groups of small cells with scanty cytoplasm reminiscent of Ewing sarcomas, a perineurioma-like pattern, a pulmonary edema-like pattern, a schwannoma-like pattern with nuclear palisading and hyalinized vessels, and reticular patterns of cells in myxoid stroma.[3,6,10,12] Occasionally, AFH may show striking nuclear pleomorphism and mitotic activity, and tumoral giant cells or reactive osteoclast-like giant cells are seen within pseudoangiomatoid spaces.[10,13] The differential diagnosis feature given such unusual histological patterns is pleomorphic malignant fibrous histiocytoma, myxofi brosarcoma, spindle cell neoplasms, myoepitheliomas, rhabdomyosarcomas, schwannomas, pleomorphic sarcomas, or Ewing sarcomas.[3,11,13] Definite diagnosis is necessary for appropriate surgical excision, because AFH is an intermediate mesenchymal malignancy with a 10% approximate rate of local recurrence and a 1% incidence of metastasis.[14]

FISH is a powerful genetic analysis tool used for the detection of various genetic abnormalities, including gene translocation, when making pathological diagnoses, especially when lesions are

small.[3,15] We presented this case to remind clinicians that AFH should be considered as a possible differential diagnosis of cutaneous soft tissue tumors, and that further diagnostic information can be obtained using FISH when the lesion is small and shows atypical histopathologic features. The translocation is not specific and is seen in other tumors such as clear cell sarcoma-like tumors of the gastrointestinal tract (CCSLGT), primary pulmonary myxoid sarcomas (PPMS), hyalinizing clear cell carcinomas (HCCC) and clear cell sarcomas. While *FUS-ATF1* fusions have so far not been detected in other neoplasms, *EWSR1-CREB1* and *EWSR1-ATF1* fusions are not unique to AFH, with CCSLGT and PPMS showing *EWSR1-CREB1* fusions, HCCC showing *EWSR1-ATF1* fusions, and clear cell sarcomas showing *EWSR1-CREB1* or *EWSR1-ATF1*.[6,16] However, we can separate these tumors from AFH clinically and histopathologically. Thus, although molecular testing is a valuable tool for diagnosis, the final diagnosis should be made in the specific clinical and pathological context.

In conclusion, the variable patterns of AFH can create significant diagnostic difficulties, and appropriate diagnoses may be missed without molecular investigation. Accurate diagnosis is particularly important because of the risk of metastasis and death from improperly treated AFH. We therefore strongly recommend a molecular confirmatory diagnostic test, such as FISH, for AFH, especially for tumors which present unusual histopathologic features.

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