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Abstract

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Atypical fibrous histiocytoma of the skin with CD30 and p80/ALK1 positivity and ALK gene rearrangement

We report the case of a two patients who presented with a solitary, asymptomatic, angiomatoid nodule on the right thigh. Histopathological finding showed a poorly circumscribed lesion, located in the dermis. The morphological aspect strongly suggested the diagnosis of atypical fibrous histiocytoma (AFH), but surprisingly, the neoplastic cells were diffusely CD30+, with a membrane staining devoid of paranuclear dot. The lesions were tested for p80/ALK1 expression. Surprisingly, we found a diffuse cytoplasmic positivity. Interestingly, using break-apart fluorescent *in situ* hybridization (FISH), we evidenced an ALK rearrangement in nearly 50% of the neoplastic cells. The expression of CD30 and ALK1 with ALK gene rearrangement raised the possibility of three diagnoses: a primary cutaneous anaplastic large cell lymphoma (ALCL), a cutaneous inflammatory myofibroblastic tumor (IMT), an AFH of the skin associated with ALK gene rearrangement and CD30 positivity. The three hypotheses were discussed and finally, although p80/ALK1 expression and cytogenetic abnormalities in fibrous histiocytoma (FH) are not yet reported to the best of our knowledge, we favored the diagnosis of AFH.

Keywords: ALK rearrangement, atypical fibrous histiocytoma, inflammatory myofibroblastic tumor, p80/ALK1 expression

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Fibrous histiocytoma (FH) is a dermal tumor characterized histopathologically by a proliferation of mononuclear, spindle-shaped or histiocytoid cells and/or multinucleated cells, often admixed with inflammatory cells. Over the years several clinicopathologic variants of FH have been delineated including cellular, aneurysmal, epithelioid, [atypical fibrous histiocytoma

(AFH); 'pseudosarcomatous,' dermatofibroma with monster cells], lipidized 'ankle-type,' palisading, cholesterotic and FH with osteoclast-like giant cells.

AFH is a rare lesion that is similar to FH most commonly presents on the extremities of young to middle-aged adults as a solitary, firm cutaneous nodule. Pathologically, this

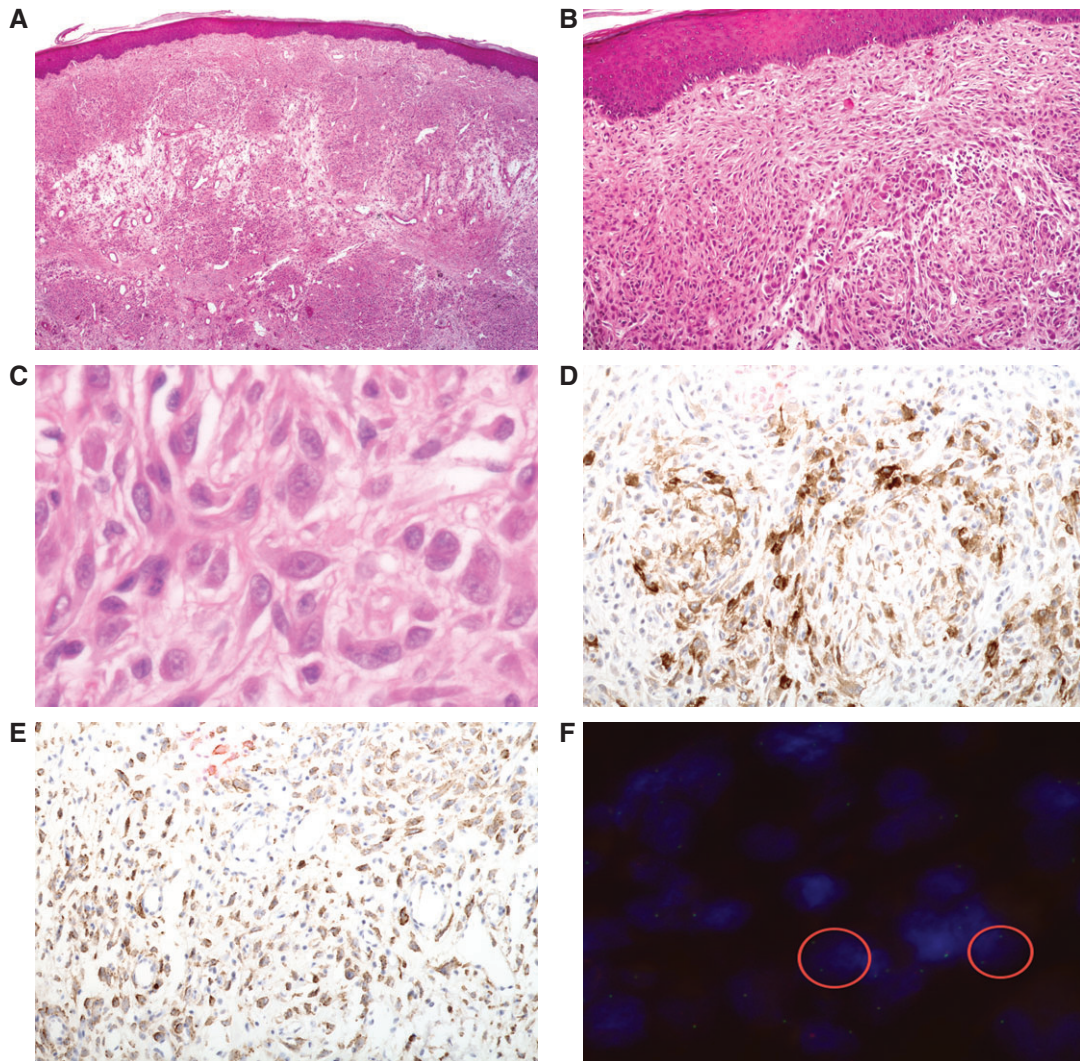


Fig. 1. A) Low power view reflects the observed morphological features, namely an intradermal lesion with normal epidermis. There is the presence of variably prominent pleomorphic, spindle (fibroblast-like), oval to round and/or polyhedral (histiocytic-like) cells with small to prominent nucleoli and abundant eosinophilic cytoplasm. B) Medium power demonstrates an intradermal tumor with normal overlying epidermis and underlying polyhedral cells. C) A high power view reveals the cytomorphology of atypical cells. D) Using immunohistochemistry, the tumor cells expressed CD30. E) Using immunohistochemistry, the tumor cells are also positive for p80/ALK1. F) FISH results using the Vysis LSI Dual Color Break Apart FISH Probe that consists of a mixture of an orange fluorochrome directed labelled 3'-ALK probe that hybridizes telomerically of the breakpoint and a green fluorochrome directed labelled 5'-ALK probe that hybridizes centromerically of the breakpoint. Note the coexistence of the fused (yellow) and slitting (red and green) hybridization signals in the nuclei of the tumour cells (red ellipse), consistent with an ALK gene rearrangement.

tumor is usually a dermal lesion with pleomorphic spindled (fibroblast-like) and polyhedral (histiocyte-like) cells admixed with multinucleate giant cells, set in a background of classic FH. Immunohistochemical analysis may not be essential for diagnosis but helps rule out other possibilities in the differential diagnosis. When completed, it typically shows focal positivity for smooth muscle actin in the spindle cell component whereas CD68 and CD163 may be focally positive usually in the multinucleated cells. The diagnosis of AFH is histomorphological and little is known about its cytogenetic abnormalities.

Herein, we report the two first cases of AFH with a positive expression of p80/ALK1 protein and a rearrangement involving *ALK* gene showed by fluorescent *in situ* hybridization (FISH).

Patient histories

Patient 1 was a 32-year-old man who presented with a solitary, asymptomatic, angiomatoid nodule on the right thigh. He had no previous medical history. Histopathologic assessment showed a poorly circumscribed lesion, localized in the dermis, without extension to the subcutis.

There was no epidermal alteration. The tumor was composed of a proliferation of large epithelioid cells with abundant eosinophilic cytoplasm. Some were stellate and other showed a histiocytoid appearance (Fig. 1A,B). They were few multinucleated cells and some resembled anaplastic, showing hyperchromatic multi-lobulated nuclei. The cells had vesicular nuclei and small to prominent nucleoli. They were admixed with spindle cells, showing fibroblast/myofibroblast morphology and few lymphocytes and histiocytes. There was a relatively low mitotic index [3 mitoses per 10 high power fields (hpf)]. Tumor stroma was fibrous with numerous dilated capillaries. These histomorphologic aspects strongly suggested the diagnosis of AFH.

Because few anaplastic cells were recognized, a phenotypic study was performed using immunohistochemistry. As expected, the neoplastic cells expressed CD10 and D2-40. Surprisingly, tumor cells were also diffusely CD30 positive with a membrane staining devoid of paranuclear dots (Fig. 1C). CD45, CD2, CD3, CD5, CD7, CD4, CD8, CD20, CD79a, CD138, PAX5, S100, MelanA, smooth muscle actin and desmin were all negative. CD168 and CD63 staining highlighted stromal histiocytes. Because of the fibroblast–myofibroblast-like component and the strong positivity for CD30, the lesion was tested for p80/ALK1 expression (Fig. 1D). Surprisingly, we found a diffuse cytoplasmic positivity. B and T-cell clonality studies performed after DNA extraction from the paraffin blocks showed a polyclonal aspect. Interestingly, using break-apart FISH, we showed an *ALK* rearrangement in nearly 50% of the neoplastic cells (Fig. 1C). The diagnosis of AFH with *ALK* gene rearrangement was rendered.

Patient 2 was a 23-year-old woman who presented with an 18-month history of an unique pinkish 7mm-nodule of the right leg. The clinician initially suspected a Spitz nevus or a clear cell acanthoma. Local excision was performed. Microscopically, the tumor was characterized by a dermis nodular fairly well-circumscribed proliferation of large epithelioid and moderately-atypical cells with scattered lymphocytes and multinucleate cells in the background. The tumor cells often had irregular nuclei, pre-eminent nucleoli and abundant cytoplasm. In immunohistochemical staining, the atypical cells were positive for CD68, CD163, CD4 and CD30. S100, HMB45, Melan-A, CD2, CD3, CD5, p63, pancytokeratin, CD31, CD34 and smooth muscle actin were all negative. The lesion was tested for p80/ALK1 expression

and showed diffuse cytoplasmic positivity. FISH analysis showed a rearrangement involving *ALK*. The diagnosis of histiocytoma with atypical cells and *ALK* rearrangement was made.

Materials and methods

The histopathologic diagnosis of AFH was made on hematoxylin/eosin/safranin-stained sections and periodic acid-Schiff-stained sections. Immunohistochemistry was carried out using an indirect immunoperoxidase method on formalin-fixed paraffin-embedded (FFPE) tissues. The following markers were used after appropriate antigen retrieval: CD20 (clone L26, Dako, Denmark A/S 1 : 500), CD79a (clone JCB117, Dako, Denmark A/S 1 : 20), Pax5 (clone SP34, Ventana Roche Diagnostics, Mannheim, Germany), CD138 (clone MI15, Dako, Denmark A/S 1 : 100), CD2 (clone MRQ-11, Ventana Roche Diagnostics, Mannheim, Germany), CD3 (clone F7238, Dako, Denmark A/S 1 : 20) CD5 (clone 4C7, Leica Microsystem, 1 Newcastle upon Tyne, United Kingdom : 100) CD7 (clone CBC-37, Dako, Denmark A/S 1 : 25), CD4 (clone SP35, Ventana Roche Diagnostics, Mannheim, Germany), CD8 (clone C8/144B, Dako, Denmark A/S 1 : 25), CD10 (clone SP67, Ventana Roche Diagnostics, Mannheim, Germany), CD30 (clone Ber-H2, Ventana Roche Diagnostics, Mannheim, Germany), CD163 (clone MRQ-26, Ventana Roche Diagnostics, Mannheim, Germany) CD68 (clone KP1, Dako, Denmark A/S 1 : 500), keratin AE1/AE3 (clone AE1/AE3, Dako, Denmark A/S 1 : 100), P63 (clone 4A4, Ventana Roche Diagnostics, Mannheim, Germany), CD31 (clone JC70A, Dako, Denmark A/S 1 : 20), CD34 (clone QBEND/10, Beckman-Coulter IMMUNOTECH SAS, Marseille, France) ALK (clone ALK1, Dako, Denmark A/S 1 : 50), smooth muscle actin (clone 1A4, Dako, Denmark A/S 1/200), desmin (clone D33, Dako, Denmark A/S 1 : 150), D240 (clone D240, Eurogentec, Dublin Ohio, USA 1 : 50), PS100 (polyclonal anti-S100, Dako, Denmark A/S 1 : 3200) , HMB45 (clone HMB45, Dako, Denmark A/S 1 : 100), MelanA (clone A103, Dako, Denmark A/S 1 : 25), KI67 (clone MIB-1, Dako, Denmark A/S 1 : 100).

Fluorescence *in situ* hybridization (FISH) analysis was performed on 3 µm tissue sections (whole sections) using the Vysis LSI ALK Break Apart Rearrangement Probe (Vysis/Abbott Molecular Diagnostics, Wiesbaden-Delkenheim, Germany) according to the manufacturer's recommendations. Slides were analyzed with

a Zeiss AxioImager Z1 fluorescence microscope (Labexchange, Burladingen, Germany) equipped with microscope-specific filters and double filter (XF53, Omega Optical, Brattleboro, VT, USA) suitable for the fluorescein isothiocyanate, Spectrum Orange and Texas Red labelled probes. Slides were analyzed independently by three scorers (Maryse Baia, Christiane Copie-Bergman, Vanessa Szablewski) with a $\times 100$ oil immersion objective. For archiving, images were captured with $\times 40$ objective using a Hamamatsu digital camera attached to the fluorescence microscope (Hamamatsu Photonics France SARL, Massy, France) and VISILOG 6.9 software (FEI, Les Ulis, France). Cases were considered positive when more than 20% of cells displayed split signals.

The detection of clonally rearranged immunoglobulin (Ig) and T-cell receptor (TCR) genes was performed using BIOMED-2 primer sets (Eurofins MWG Operon, Ebesberg, Germany) and conditions. DNA was extracted from non-microdissected FFPE tissue sections. In each case, polymerase chain reaction (PCR) amplification was carried out in duplicate. The PCR products of Ig/TCR genes were analyzed for clonality assessment by GeneScanning (Eurofins GeneScan, Metairie, Louisiana, USA).

Discussion

FH is the most common mesenchymal neoplasm of the skin. To date, the precise line of differentiation is uncertain. Clinically, most lesions present as a solitary red or brown nodules on the extremities of young to middle-aged adults. Microscopic features usually show an ill-defined dermal tumor characterized by a proliferation of mononuclear histiocytoid and stellate or spindle-shaped cells admixed with few multinucleated and inflammatory cells. Several clinicopathologic variants of FH have been delineated.

AFH is a rare variant of cutaneous FH also called *pseudosarcomatous fibrous histiocytoma* or *dermatofibroma with monster cells*. It was first described in 1983.¹ This tumor is seen as a solitary firm cutaneous nodule in a broad age range (5–79 years; median: 38 years). Anatomic distribution is wide with most cases occurring in the lower and upper extremities (79%).² Lesion size ranges from 0.4 to 8 cm (median 1.5 cm). AFH usually presents as a dermal lesion with pleomorphic atypical cells set in a background of typical FH. The pleomorphic cells are spindled, oval to round and/or polyhedral. The pleomorphic cells have large, irregular (round

to oval, cigar-shaped or bizarre), sometimes hyperchromatic, nuclei with small to prominent nucleoli and often abundant eosinophilic cytoplasm.² Variably prominent multinucleate giant cells, commonly exhibiting foamy or hemosiderin-rich cytoplasm, may be present. Mitotic figures may range from 1 to 15/10 hpf. There is a spectrum from lesions showing only focal mild pleomorphism to those exhibiting marked pleomorphism. Superficial involvement of the subcutis is seen in one third of the cases. Immunohistochemically, the tumor cells are positive for vimentin and negative for S100 protein, epithelial membrane antigen, cytokeratin and HMB45. Alpha smooth muscle actin, desmin and CD34 are sometimes focally positive. CD68 and CD163 may be focally positive, usually in multinucleated cells.³ The spindle cells can show focal positivity for smooth muscle actin and usually express D2-40.⁴ Positivity for CD68 and factor XIIIa are variable. MiB1 is expressed in less than 10% of the cells.

Histopathologically, AFH should be differentiated from a number of benign and malignant cutaneous tumors with pleomorphic and/or anaplastic cytomorphology including melanoma, spindle cell squamous cell carcinoma or primary cutaneous anaplastic large cell lymphoma (ALCL). In our cases, melanocytic and epithelial lesions were ruled out because of the negativity for corresponding markers.

The expression of CD30 and ALK1 with *ALK* gene rearrangement raised the possibility of a primary cutaneous anaplastic large cell lymphoma (ALCL). Patient 2 was first misdiagnosed as ALCL, but after hematologic evaluation and expert histopathologic evaluation, this diagnosis was revised. For patient 1, the possibility of ALCL was ruled out because of the histopathologic findings, the lack of expression of all leukocyte and T-cell markers, and the absence of a clonal rearrangement of T-cell receptor (TCR) genes. The diagnosis of *unusual fibrohistiocytic/fibroblastic tumor with ALK gene rearrangement* was thus proposed, allowing us to discuss an AFH of the skin or a cutaneous inflammatory myofibroblastic tumor (IMT) associated with *ALK* gene rearrangement and CD30 positivity.

IMT is characterized by a proliferation of myofibroblasts set in a myxoid to collagenous stroma with a prominent polymorphous inflammatory infiltrate. Although the lung is the best known and most common site,⁵ IMT can occur in many organs. Only few cases occurring in the skin have been previously reported, so that cutaneous IMT should be considered as

a diagnosis of exclusion.^{6–8} The spindle cells usually express vimentin and smooth muscle actin and approximately 50% of IMT are positive for p80/ALK1. P80/ALK1 expression in IMT reliably predicts the presence of an *ALK* gene rearrangement, which can be detected by FISH or reverse transcription-polymerase chain reaction (RT-PCR).

Although p80/ALK1 expression and cytogenetic abnormalities in FH have not yet been reported to the best of our knowledge, we favor the diagnosis of AFH in both tumors, as this fits with the clinical presentation, the histopathologic features and the negativity for smooth muscle markers that should be present in IMF. Little is known about chromosomal abnormalities in FH. Nevertheless the molecular genetics of angiomatoid FH have become increasingly understood. Angiomatoid FH was reported in 1979 by Enzinger as a variant of malignant fibrous histiocytoma [angiomatoid malignant fibrous histiocytoma (MFH)], which showed a predilection for extremities and occurred at much younger age than other subtypes of MFH. A number of reports describe *EWSR1/CREB1*, *EWSR1/ATF1* and *FUS/ATF1* gene fusions^{9,10} in this context. About 93% of angiomatoid FH have a rearrangement of *EWSR1* (as manifested by the *EWSR1/CREB1* and *EWSR1/ATF1* fusion genes), whereas about 7% of cases have a rearrangement of *FUS*. FISH for *EWSR1* and

FUS is widely available and is used routinely in medical centers that encounter large numbers of sarcomas/mesenchymal neoplasms.

Unfortunately, the designation angiomatoid FH is confusing, as this tumor is not a variant of FH and has no relation with aneurysmal FH. Angiomatoid FH has therefore been recognized as a distinct clinicopathologic entity by the World Health Organization (WHO) classification of the tumors of soft tissue and has been designated a tumor of intermediate malignancy.

Interestingly, abnormal p80/ALK1 expression with a variety of structural chromosomal changes have been shown to be present in a wide variety of soft tissue tumors, especially rhabdomyosarcoma and malignant peripheral nerve sheath tumor (MPNST).^{11,12} Nevertheless, with the exception of IMT, in all others soft tissue tumors with abnormal p80/ALK1 expression, the corresponding chromosomal abnormality was two or multiple fused ALK signal using break-apart *ALK* probe without gene rearrangement. Moreover, MFH is one of the differential diagnoses of AFH, and even if it could show p80/ALK1 positivity by immunochemistry, no *ALK* gene rearrangement would have been showed.

In conclusion, we report the two first diagnoses of AFH with *ALK* gene rearrangement.

The exact frequency of p80/ALK1 expression and *ALK* rearrangement in FH needs further investigation.

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