Modern Pathology (2015) 28, 904–912

ALK rearrangement and overexpression in epithelioid fibrous histiocytoma

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Epithelioid benign fibrous histiocytoma, also known as 'epithelioid cell histiocytoma,' has traditionally been considered a morphologic variant of cutaneous fibrous histiocytoma (dermatofibroma). In addition to its characteristic epithelioid cytomorphology, several phenotypic differences suggest that epithelioid fibrous histiocytoma may differ biologically from other variants. Recently, *ALK* rearrangement was described in two cases of epithelioid fibrous histiocytoma and separately in two cases reported as 'atypical' fibrous histiocytoma (with epithelioid features), with corresponding ALK expression detectable by immunohistochemistry. The goals of this study were to determine the frequency of ALK expression by immunohistochemistry in epithelioid fibrous histiocytoma, to determine its value for the diagnosis of epithelioid fibrous histiocytoma among variants and other histologic mimics, and to evaluate *ALK* gene rearrangement in epithelioid fibrous histiocytoma. ALK protein expression was evaluated in whole tissue sections from 33 epithelioid fibrous histiocytomas, 41 other cases of fibrous histiocytoma (11 conventional and 10 each cellular, atypical, and aneurysmal types), 10 cutaneous syncytial myoepitheliomas, and 5 atypical fibroxanthomas, using a mouse anti-ALK monoclonal antibody. Fluorescence *in situ* hybridization (FISH) was performed using break-apart probes. In total, 29/33 (88%) cases of epithelioid fibrous histiocytoma showed diffuse cytoplasmic ALK expression. Staining was moderate to strong in intensity in all cases except one, which showed diffuse weak expression. All other tumor types were negative for ALK expression. FISH demonstrated *ALK* rearrangement in all ALK-immunoreactive cases evaluated ($n = 13$), and not in one ALK expression-negative epithelioid fibrous histiocytoma successfully examined. In conclusion, the majority of epithelioid fibrous histiocytomas demonstrate ALK expression and *ALK* gene rearrangement. ALK expression is not seen in other variants of fibrous histiocytoma, providing a useful diagnostic tool to distinguish epithelioid fibrous histiocytoma from most histologic mimics. The expression of ALK suggests that epithelioid fibrous histiocytoma is a biologically distinct tumor type, unrelated to conventional fibrous histiocytoma and histologic variants.
Modern Pathology (2015) **28,** 904–912; doi:10.1038/modpathol.2015.49; published online 10 April 2015

Epithelioid benign fibrous histiocytoma, also known as 'epithelioid cell histiocytoma,' has traditionally been considered a morphologic variant of cutaneous fibrous histiocytoma with prominent epithelioid cytomorphology. While some conventional/regular fibrous histiocytomas (and variants) can show focal epithelioid features, the diagnosis of epithelioid fibrous histiocytoma has been reserved for those tumors with at least 50% epithelioid morphology.[1,2] Clinically, epithelioid fibrous histiocytoma most commonly presents as a flesh-colored nodule on the extremities of young- to middle-aged adults.[1–3] Epithelioid fibrous histiocytoma is usually exophytic and well circumscribed with an epidermal collarette at the edges of the lesion, and is composed of a relatively monotonous intradermal population of polygonal cells with moderate amounts of eosinophilic or amphophilic cytoplasm, vesicular nuclei, and small nucleoli.[1–6] Many of the tumor cells occur as binucleate or trinucleate forms, but multinucleate giant cells are less common than in regular fibrous histiocytoma. The stroma of epithelioid fibrous histiocytoma is often richly vascular, consisting of small thin-walled vessels and larger thick-walled vessels. Prominent perivascular accentuation of tumor cells is often seen, typically with a whorled growth pattern. Epithelioid fibrous histiocytoma also differs from regular fibrous histiocytoma in that it tends to lack lateral entrapment of collagen, and usually lacks a prominent infiltrate of foamy histiocytes and lymphocytes.

Such differences have led some authors to suggest that epithelioid fibrous histiocytoma may be a

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Received 15 January 2015; revised 6 March 2015; accepted 7 March 2015; published online 10 April 2015

distinct entity, biologically different from regular fibrous histiocytoma.[2,3] Recently generated molecular data support this interpretation: recurrent gene fusions involving protein kinase C isoforms have been identified in regular fibrous histiocytoma.[7] In contrast, molecular analyses of epithelioid fibrous histiocytoma have identified *ALK* gene rearrangements, although the data available are very limited. Two cases have been studied by next-generation sequencing, which surprisingly identified the fusion genes *VCL-ALK* and *SQSTM1-ALK* (one case each).[8] Two prior lesions diagnosed as 'atypical' fibrous histiocytoma were reported to show *ALK* rearrangement[9] and also appear to represent examples of epithelioid fibrous histiocytoma. Corresponding ALK expression was detectable by immunohistochemistry in these four cases.

To date, the only consistent immunohistochemical marker to help in the diagnosis of epithelioid fibrous histiocytoma is EMA, which is expressed in ~65% of cases;[3] however, this marker is nonspecific and its sensitivity for this diagnosis is relatively low. The goal of this study was to determine the frequency of ALK expression and *ALK* rearrangement in a large series of epithelioid fibrous histiocytoma, in comparison with other fibrous histiocytoma variants and potential histologic mimics.

Materials and methods

Cases were retrieved from the surgical pathology and consult files of Brigham and Women's Hospital, Boston, MA, USA and the consult files of one of the authors (CDMF). In total, 89 tumors were evaluated: 33 epithelioid fibrous histiocytomas (5 previously reported[3]), 11 conventional/regular fibrous histiocytomas, and 10 each cellular, atypical, and aneurysmal types, as well as five atypical fibroxanthomas and 10 cutaneous syncytial myoepitheliomas. Representative hematoxylin and eosin-stained slides were reviewed to confirm the diagnoses.

Immunohistochemistry was performed on 4-μm-thick formalin-fixed paraffin-embedded whole tissue sections following pressure cooker antigen retrieval (0.01 M citrate buffer, pH 6.0) using a mouse anti-ALK monoclonal antibody (1:50 dilution; 40 min incubation; clone 5A4; Leica Biosystems, Newcastle Upon Tyne, UK). Immunohistochemistry for ROS1 was performed on cases negative for ALK expression following pressure cooker antigen retrieval using a rabbit anti-ROS1 monoclonal antibody (1:100 dilution; 40 min incubation; clone D4D6; Cell Signaling Technology, Danvers, MA, USA). Immunohistochemistry for CD30 (1:40 dilution; clone Ber-H2; Dako, Carpinteria, CA, USA) was performed on a subset of cases ($n=8$) positive for ALK expression. The results were scored as positive or negative, and the pattern and intensity of staining were recorded.

Dual-color fluorescence *in situ* hybridization (FISH) was performed on 4 μm sections in 18 cases: 14 epithelioid fibrous histiocytomas with ALK expression and 4 cases without ALK expression. Targeted tumor areas were circled following review of the corresponding H&E slide. Tissue sections were baked overnight at 56 °C, deparaffinized by three consecutive 15 min immersions in xylene, and dehydrated twice in 100% ethanol for 2 min. The slides were then immersed in TRIS-EDTA (100 mM Tris base, 50 mM EDTA, pH 7.0) for 1 h at 95–99 °C and rinsed in PBS for 5 min. Proteolytic digestion of the sections was performed using Digest-All 3 Pepsin solution (Invitrogen, Camarillo, CA, USA) at 37 °C for 10–20 min, twice. The sections were then sequentially dehydrated in alcohol (70, 85, 95, and 100% for 2 min each) and air-dried. The LSI *ALK* dual-color break-apart probe (Abbott Molecular, Des Plaines, IL, USA) was applied and denatured at 94 °C for 4 min. Hybridization was carried out overnight in a humidified chamber at 37 °C. Post-hybridization wash was performed in 0.5 × SSC, pH 7.0 at 74 °C for 5 min. Slides were counterstained with DAPI. Results were analyzed with a fluorescence Leica microscope, and representative images were captured. Samples were classified as positive for *ALK* rearrangement when $\geq$10% of nuclei showed split signals or single red signals (3′ *ALK*) were observed. Four cases (one positive for ALK expression and three negative for ALK expression by immunohistochemistry) were deemed insufficient for FISH due to technical reasons (either poor hybridization or insufficient tissue). Non-neoplastic diploid cells were abundant in every case and were used as internal controls.

Results

Cases of epithelioid fibrous histiocytoma were typically well circumscribed and composed of a monotonous intradermal population of polygonal cells with palely eosinophilic cytoplasm, minimal nuclear atypia, frequent binucleate cells, and prominent thin-walled vessels.

The results of ALK immunohistochemistry are summarized in Table 1. Twenty-nine of 33 cases of epithelioid fibrous histiocytoma (88%) showed diffuse cytoplasmic staining for ALK (Figures 1 and 2), which was moderate to strong in intensity in all cases except one, which showed diffuse weak expression. Of the four cases negative for ALK expression, one tumor located on the shin contained numerous lipidized cells, reminiscent of lipidized fibrous histiocytoma, as well as a population of epithelioid cells with frequent binucleate forms, which were indistinguishable from those seen in other cases of epithelioid fibrous histiocytoma (Figure 3a and b). Another ALK expression-negative case showed a somewhat more solidly cellular growth pattern without the prominent vessels usually seen in epithelioid fibrous histiocytoma but was otherwise indistinguishable from ALK expression-positive

Table 1 Summary of immunohistochemical staining for ALK in epithelioid fibrous histiocytoma and other tumor types

Tumor type	*Total cases*	*ALK positive (%)*
Epithelioid fibrous histiocytoma	33	29 (88)
Aneurysmal fibrous histiocytoma	10	0 (0)
Atypical fibrous histiocytoma	10	0 (0)
Atypical fibroxanthoma	5	0 (0)
Cellular fibrous histiocytoma	10	0 (0)
Conventional fibrous histiocytoma	11	0 (0)
Cutaneous syncytial myoepithelioma	10	0 (0)

cases (Figure 3c and d). Of the remaining two cases, one was a superficial biopsy, and the other showed superimposed reactive changes. All other types of fibrous histiocytoma (Figure 4) and other tumor types evaluated (Figure 5) were negative for ALK expression. The four cases that lacked ALK expression were also negative for ROS1 by immunohistochemistry. Of eight cases evaluated for CD30 expression, five (62%) were positive; four showed multifocal staining of weak to moderate intensity, and one showed only rare positive cells.

FISH demonstrated *ALK* rearrangement in all ALK-immunoreactive cases successfully examined ($n=13$); 12 cases demonstrated an apparently balanced *ALK* rearrangement (split red and green signals and a pair of fused signals; Figure 6a), whereas in one case the rearrangement was unbalanced (with loss of the 5′ signal; Figure 6b). The percentage of nuclei with the rearrangement ranged from 20 to 70%, suggesting the presence of numerous non-neoplastic (likely inflammatory and endothelial) cells within the lesion. *ALK* rearrangement was not seen in one ALK expression-negative epithelioid fibrous histiocytoma.

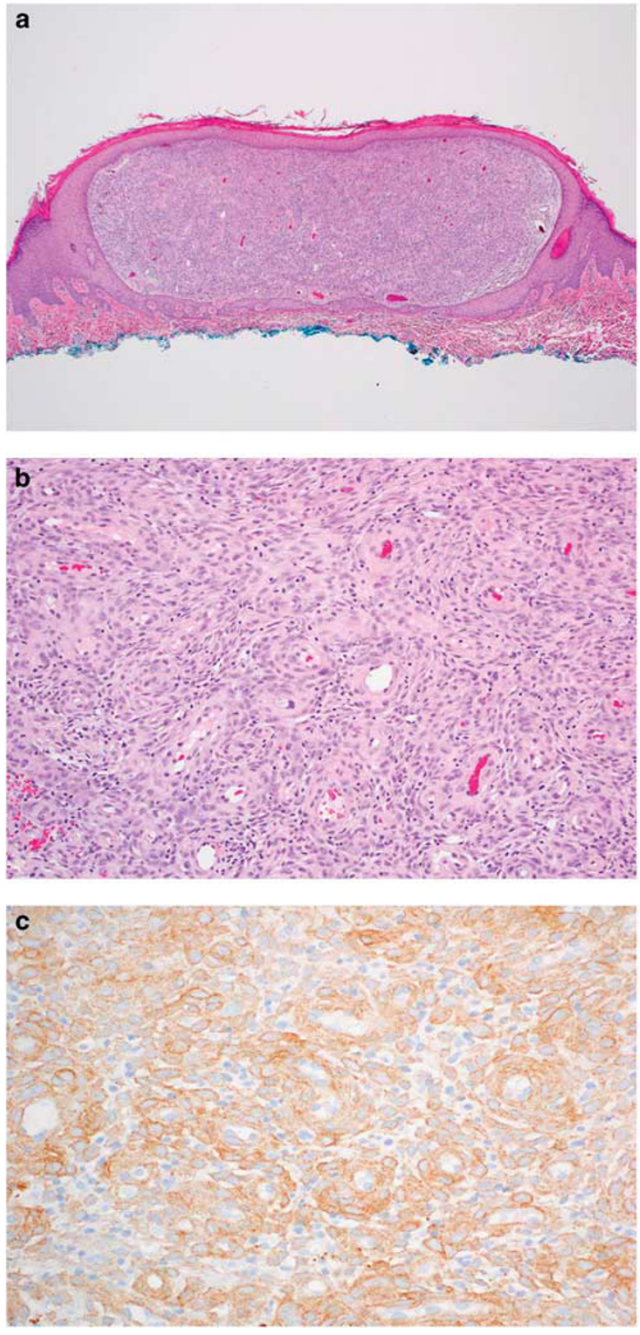

Figure 1 Epithelioid fibrous histiocytoma is usually exophytic and well circumscribed with an epidermal collarette (**a**). The tumor often has prominent small thin and thick-walled vessels, and is composed of polygonal or ovoid cells with variable amounts of palely eosinophilic cytoplasm, vesicular nuclei, and generally small or inconspicuous nucleoli; admixed lymphocytes are present (**b**). Tumor cells show diffuse expression of ALK (**c**).

Discussion

Epithelioid fibrous histiocytoma was first described in 1989 by Wilson Jones *et al* in a series of 19 cases.[1] It was proposed that these tumors represent a variant of fibrous histiocytoma owing to similar clinical features and some overlapping immunohistochemical findings, such as the presence of FXIIIa expression and the absence of S100 protein expression in lesional cells. Several groups have since described consistent and distinctive histologic findings in epithelioid fibrous histiocytoma, and due to striking morphologic and immunophenotypic differences with regular fibrous histiocytoma, some authors have suggested that this tumor type may in fact be distinct from regular fibrous histiocytoma and its other variants.[2,3] The classic histologic features of epithelioid fibrous histiocytoma have been described in detail; these usually exophytic, well circumscribed tumors consist of an intradermal proliferation of relatively uniform epithelioid to polygonal cells with vesicular nuclei and moderate amounts of eosinophilic or amphophilic cytoplasm. The tumor cells are frequently binucleate; multinucleate giant cells are less common than in regular fibrous histiocytoma. In contrast to other variants of

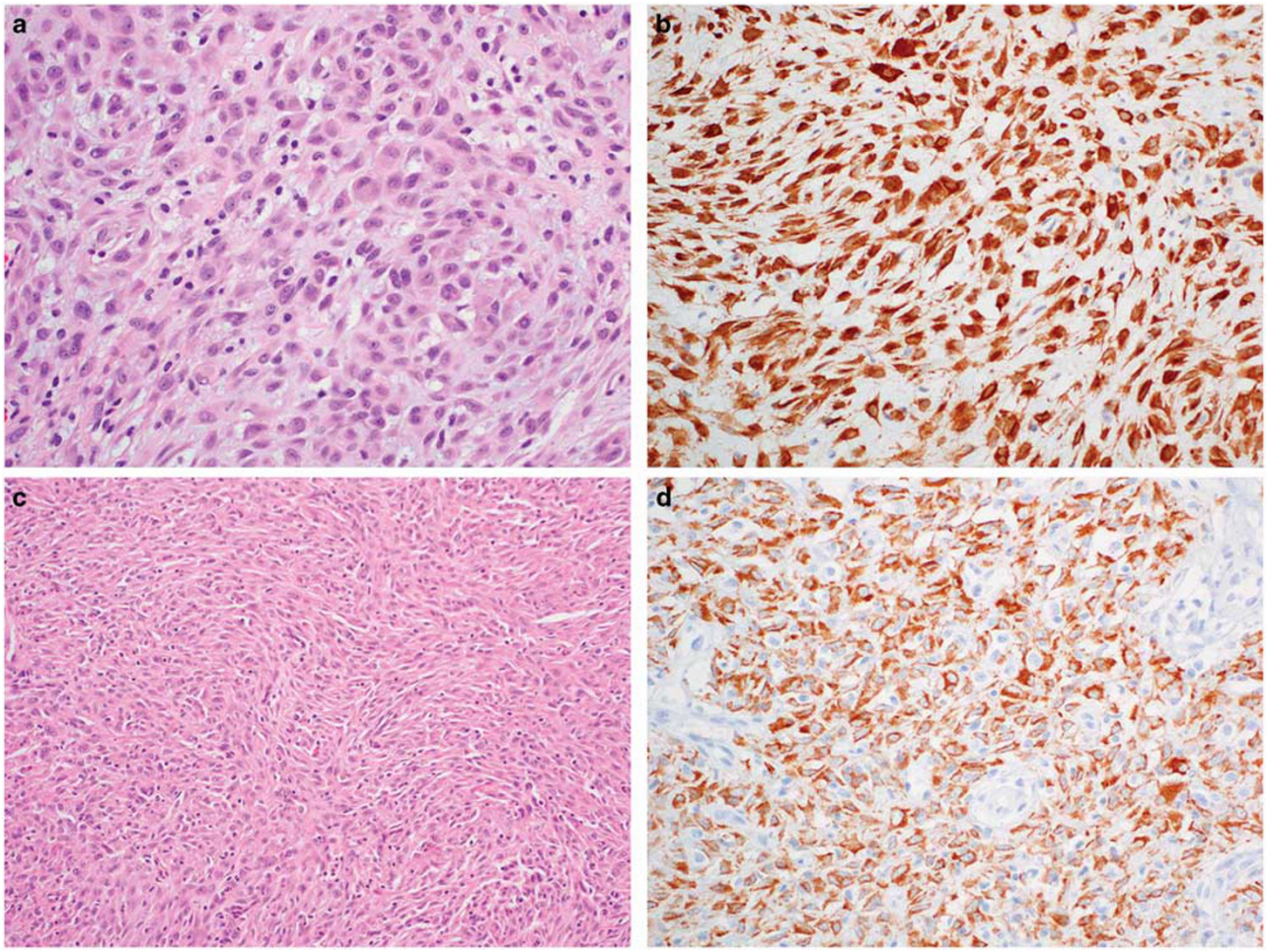

Figure 2 Binucleate tumor cells are commonly present in epithelioid fibrous histiocytoma and may be a helpful clue to the diagnosis (**a**); cytoplasmic expression of ALK is seen in this case (**b**). Epithelioid fibrous histiocytoma with a fibrous stroma and focally spindled morphology (**c**); tumor cells are diffusely positive for ALK expression (**d**).

fibrous histiocytoma, expression of EMA is present in ~65% of cases.[3] In addition, the tumor cells are usually negative for SMA and desmin, in contrast to regular fibrous histiocytoma, which shows variable expression of these markers.[10,11]

Regular fibrous histiocytoma and other morphologic variants (cellular, aneurysmal, atypical, deep, lipidized) are composed of a variable admixture of mononuclear and multinucleate cells with a histiocytoid and/or myofibroblastic appearance. The precise histotype of the lesional cells has been long debated, despite early ultrastructural analysis demonstrating fibroblastic and histiocytic cellular features.[12] In addition, until relatively recently, the nature of this lesion as a reactive process or a true neoplasm was also controversial. The identification of recurrent translocations in this tumor type has confirmed the neoplastic nature of fibrous histiocytoma: in regular fibrous histiocytoma, the fusion genes involve the protein kinase C isoform-encoding *PRKCB* and *PRKCD*, with genes encoding membrane-associated proteins (*PDPN, CD163*, and *LAMTOR1*), which result in constitutive activity of PKC.[7] The well documented, although extremely rare, occurrence of metastases of morphologically benign-appearing fibrous histiocytomas also supports a neoplastic process.[13–15]

ALK rearrangement and ALK overexpression were very recently described in two cases of epithelioid fibrous histiocytoma, owing to the presence of the fusion genes *VCL-ALK* and *SQSTM1-ALK*.[8] In addition, in a separate study, *ALK* rearrangement was described in two tumors reported as 'atypical fibrous histiocytoma'; however, according to the morphologic description ('with epithelioid features') and the histologic images in that study, those two lesions may actually represent examples of epithelioid fibrous histiocytoma.[9] In the present study, we found ALK expression in 88% of epithelioid fibrous histiocytomas, which is therefore the most consistent immunohistochemical finding to date in these tumors. ALK overexpression correlated with *ALK*

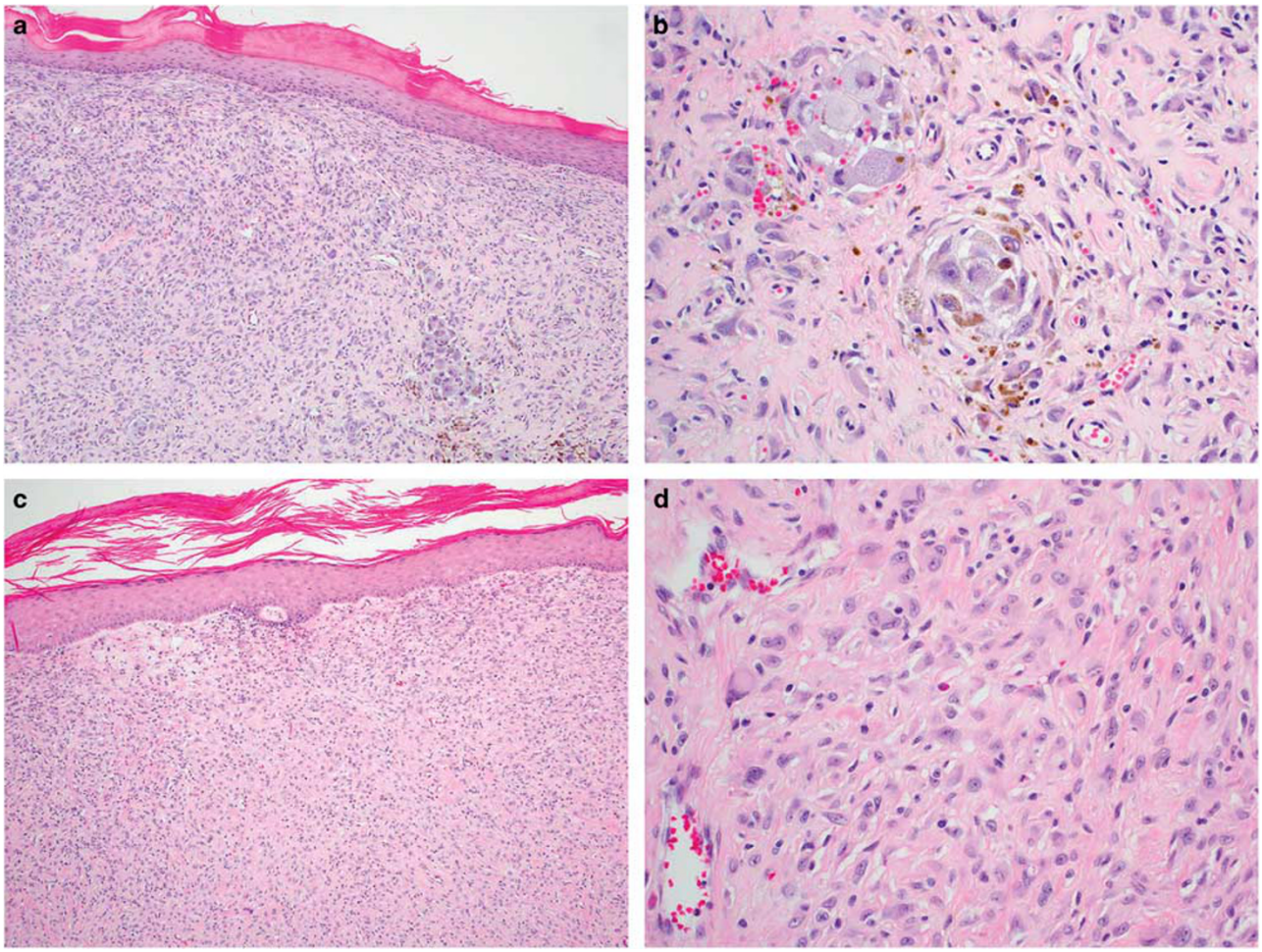

Figure 3 ALK expression-negative epithelioid fibrous histiocytomas. One tumor arose on the shin and contained numerous lipidized cells, as well as epithelioid cells with binucleation; this tumor may represent an unusual lipidized fibrous histiocytoma with epithelioid features (**a**, **b**). Another case showed a somewhat more solidly cellular growth pattern without the prominent vessels usually seen in epithelioid fibrous histiocytoma (**c**); however, the cytomorphology of the tumor cells was indistinguishable from other cases of epithelioid fibrous histiocytoma, and frequent binucleate forms were present (**d**).

rearrangement. Of the four previously reported cases of epithelioid fibrous histiocytoma with *ALK* rearrangement, three had expression of CD30, ranging from focal and weak[8] to diffuse and strong[9] in distribution and intensity. We evaluated a subset of cases in our series with CD30 ($n = 8$) and found CD30 expression in five cases (62%), which was usually multifocal in distribution, and weak to moderate in intensity. The apparent relationship between ALK and CD30 expression in this and in other tumor types[16,17] is notable but poorly understood at this time. Very recently, ROS1 has been identified as an alternate kinase driver to ALK in a subset of lung adenocarcinomas and inflammatory myofibroblastic tumors,[18,19] and immunohistochemistry for ROS1 has been shown to correlate with *ROS1* rearrangement.[20] We evaluated ROS1 expression in the four epithelioid fibrous histiocytoma cases that were negative for ALK expression; all were negative for ROS1, arguing against an underlying *ROS1* rearrangement. Of the four ALK expression-negative cases in this study, only one stood out as having significant morphologic differences: this tumor arose on the shin and was predominantly composed of epithelioid cells with frequent binucleate forms, but also contained numerous lipidized cells; it is possible that this case instead represents an unusual lipidized fibrous histiocytoma with epithelioid features.

The identification of *ALK* fusions in epithelioid fibrous histiocytoma shows that this tumor type differs not only morphologically from regular fibrous histiocytoma, but also biologically. It also further illustrates the remarkable plasticity of ALK as an oncogenic driver in morphologically and clinically distinct tumor types. The fusion genes previously described in epithelioid fibrous histiocytoma also occur in a variety of other neoplasms: *VCL-ALK* has been described in a morphologically distinctive and

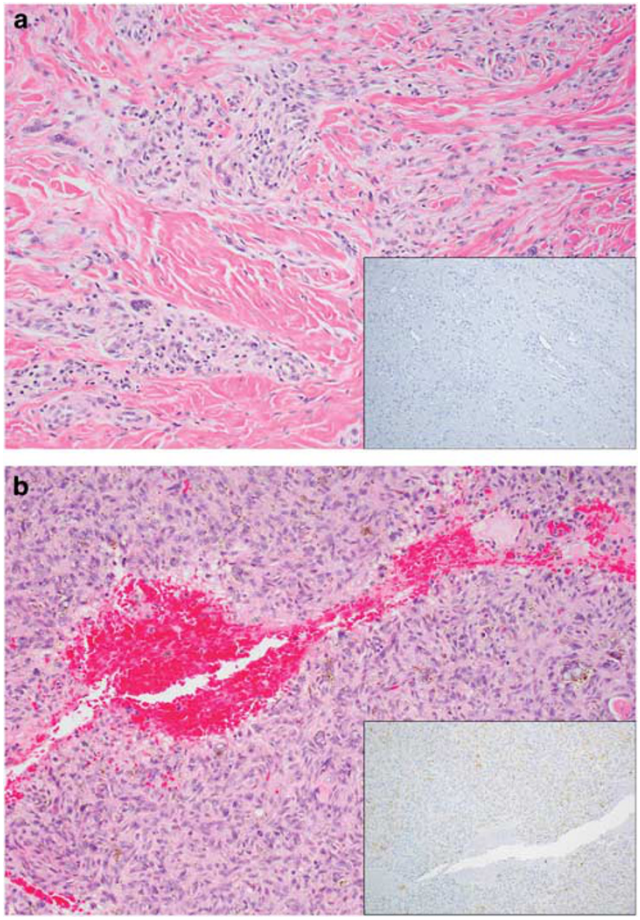

Figure 4 Atypical fibrous histiocytoma showing entrapment of collagen and scattered large atypical cells (**a**). Tumor cells are negative for ALK expression (inset). Aneurysmal fibrous histiocytoma with hemosiderin deposition (**b**) is also negative for ALK expression (inset).

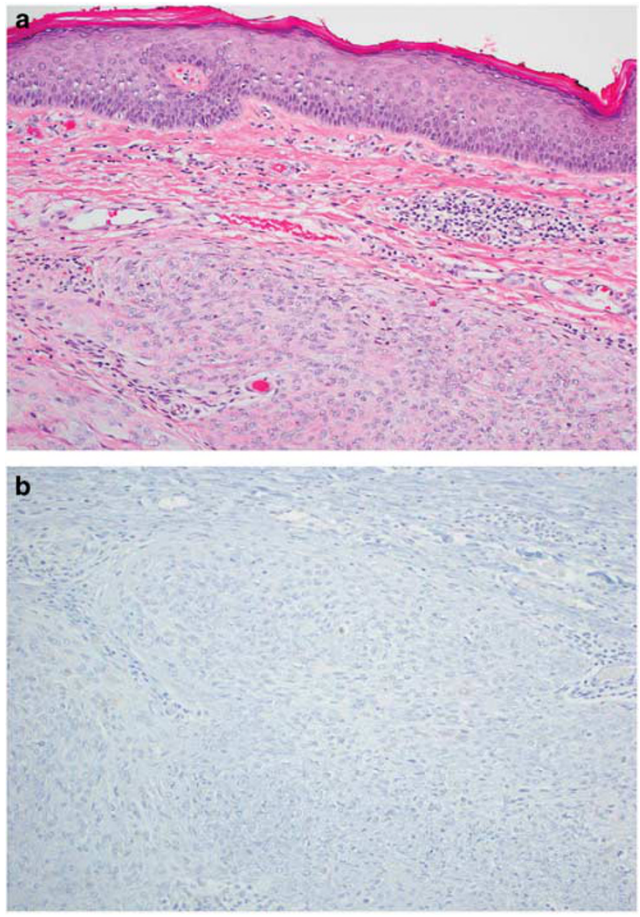

Figure 5 Cutaneous syncytial myoepithelioma often mimics epithelioid fibrous histiocytoma, being composed of a solid proliferation of ovoid cells with moderate amounts of palely eosinophilic cytoplasm (**a**). Tumor cells lack expression of ALK (**b**), which helps distinguish these two tumor types.

clinically aggressive group of renal cell carcinomas arising in young patients with sickle cell trait,[21–23] and *SQSTM1-ALK* in two cases of ALK-immunoreactive large B-cell lymphoma.[24,25] Activated ALK, usually in the form of highly expressed chimeric oncoproteins, is the main oncogenic driver of these neoplasms, which are hence sensitive to therapeutic inhibition with ALK-specific small molecule inhibitors.[26] Epithelioid fibrous histiocytoma is a benign tumor, which virtually always pursues an indolent clinical course; however, the extremely rare occurrence of metastasis of morphologically benign fibrous histiocytoma has been described in one case showing epithelioid morphology.[14] Although extremely rare, the identification of *ALK* fusion genes in this tumor type provides a potential therapeutic target in such exceptional cases.

The epithelioid nature of this cutaneous lesion raises a relatively discrete group of potential differential diagnostic considerations. Cutaneous syncytial myoepithelioma is probably the neoplasm most likely to be confused with epithelioid fibrous histiocytoma. This benign neoplasm arises in the superficial dermis, usually on the extremities of young- to middle-aged adults, and is composed of sheets of relatively uniform, bland, ovoid, spindled or histiocytoid cells with palely eosinophilic syncytial cytoplasm and vesicular nuclei with small or inconspicuous nucleoli.[27] *EWSR1* rearrangement is present in the vast majority of these tumors,[27] but FISH is rarely needed as a diagnostic tool. Similar to epithelioid fibrous histiocytoma, cutaneous syncytial myoepithelioma shows expression of EMA, which is found in nearly all cases. Unlike epithelioid fibrous histiocytoma, immunoreactivity for S100 is observed in the majority of cases, but may sometimes be limited in extent, and less commonly, expression of other myoepithelial markers GFAP, SMA, and p63 is seen,[27] all of which are negative in epithelioid fibrous histiocytoma.[3] In this study, all syncytial myoepitheliomas examined for expression of ALK were negative. ALK expression is therefore a helpful marker to distinguish epithelioid fibrous histiocytoma from cutaneous syncytial myoepithelioma.

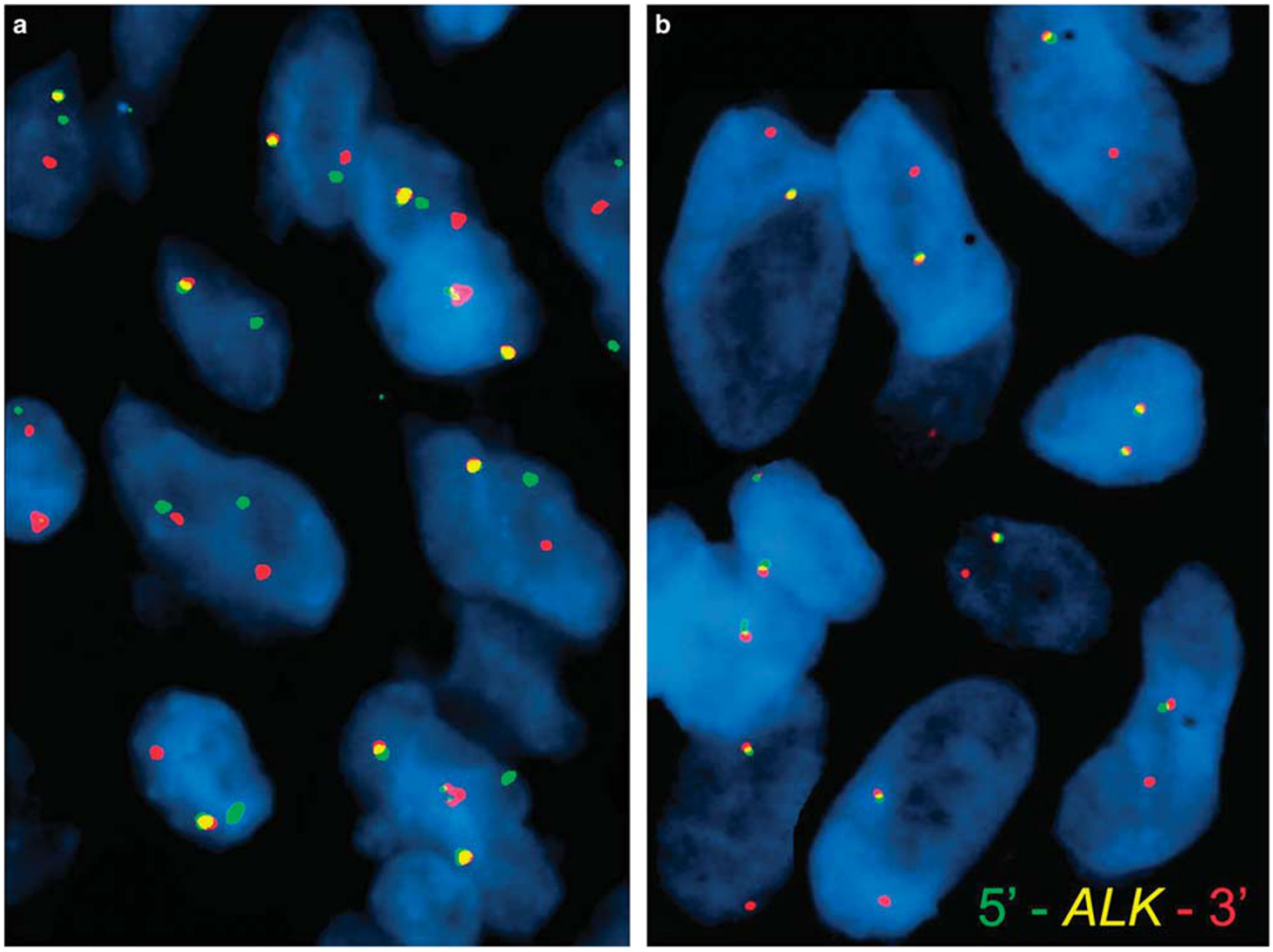

Figure 6 *ALK* rearrangement in epithelioid fibrous histiocytomas demonstrated by FISH. The tumor cell nuclei show a fused signal pair, and abnormally split red and green signals, indicative of a genomic *ALK* rearrangement (**a**). In one case, the 5′ (centromeric) probe was lost in tumor cell nuclei, a pattern consistent with unbalanced *ALK* rearrangement (**b**).

Occasionally, epithelioid fibrous histiocytoma may mimic epithelioid sarcoma. The high frequency of EMA expression in both tumor types is also a potential diagnostic pitfall. Clinically, like epithelioid fibrous histiocytoma, epithelioid sarcoma typically presents as a nodule on the extremities of young adults, and although it tends to arise in deeper dermis and subcutis, it may involve superficial dermis, where it is usually less sharply circumscribed than epithelioid fibrous histiocytoma.[28,29] The tumor cells of epithelioid sarcoma are variably epithelioid and spindled in appearance, with abundant pink cytoplasm and vesicular nuclei with small nucleoli, and although relatively uniform, they show greater nuclear atypia than epithelioid fibrous histiocytoma. In addition to EMA, the tumor cells of epithelioid sarcoma also express cytokeratins and CD34, and loss of INI1 (SMARCB1) expression is seen in >90% of cases.[30,31] Immunohistochemistry therefore readily distinguishes these two tumor types.

Epithelioid fibrous histiocytoma shares *ALK* rearrangement with Spitz nevus, another cutaneous neoplasm that may enter the differential diagnosis with epithelioid fibrous histiocytoma. Spitz nevi are benign melanocytic neoplasms that appear as flesh-colored papules or nodules on the extremities, head and neck or trunk of young patients. Spitz nevi are composed of either purely epithelioid or spindled melanocytes, or a mixture of both, and are usually amelanotic. Most Spitz nevi have a junctional component, but some are entirely intradermal. Similar to epithelioid fibrous histiocytoma, Spitz nevi are well circumscribed and contain epithelioid cells that show minimal cytologic atypia or pleomorphism. Histologic features that favor Spitz nevus over epithelioid fibrous histiocytoma include a nested growth pattern, a junctional component (if present) with pagetoid spread of nevus cells, Kamino body formation, and maturation of nevus cells toward the base of the lesion. It is now known that over 50% of Spitz nevi harbor fusions involving the kinases *ALK, ROS1, NTRK1, BRAF,* and *RET*.[32] Those tumors with *ALK* rearrangement (~10%) show corresponding overexpression of ALK by immunohistochemistry. The *ALK* fusion partners in Spitz

nevi have been identified as *TPM3* (tropomyosin 3) and *DCTN1* (dynactin 1).[33] ALK immunohistochemistry alone is therefore not sufficient to distinguish between these two tumor types. However, the tumor cells of Spitz nevus are positive for S100 protein and melan A, show variable expression of HMB45, and are negative for EMA.[34] In contrast, the tumor cells in epithelioid fibrous histiocytoma are consistently negative for S100 protein and melan A.[3,35]

In summary, we demonstrate consistent ALK expression and *ALK* gene rearrangement in epithelioid fibrous histiocytoma, which are not seen in other fibrous histiocytoma variants. The significance of these findings can be considered at three different levels: (1) nosologically, suggesting that epithelioid fibrous histiocytoma is a distinct tumor type, biologically unrelated to other variants of cutaneous fibrous histiocytoma; (2) diagnostically, providing a useful marker to distinguish epithelioid fibrous histiocytoma from histologic mimics; and (3) biologically, further illustrating the remarkable plasticity of ALK as an oncogenic driver, and highlighting the diverse role of similar genetic changes in different histologic entities.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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