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Atypical fibroxanthoma with lymphomatoid reaction

Background: Atypical fibroxanthoma (AFX) represents an uncommon skin tumor typically occurring on sun-damaged skin of the elderly. Histopathologic variants include spindled, clear cell, osteoid, osteoclastic, chondroid, pigmented, granular cell and myxoid lesions. To date, an atypical lymphoid infiltrate, including CD30-positive large cells mimicking lymphomatoid papulosis, has not been described in association with AFX.
Methods: The clinical and histopathological characteristics of two AFX cases inciting an atypical lymphoid infiltrate, along with immunohistochemical profiles and T-cell receptor gamma (*TCRγ*) gene rearrangement results, were reviewed.
Results: Lesions in both cases occurred as solitary nodules in elderly patients. Microscopically, both lesions showed a cellular proliferation composed of pleomorphic spindle cells, associated with a prominent intralesional atypical lymphoid infiltrate. The spindle cells expressed CD10 but lacked the expression of S-100, cytokeratins and muscle markers, thereby confirming the diagnosis of AFX. CD30 highlighted a significant subset of large mononuclear cells in the lymphoid infiltrate of one case. *TCRγ* gene rearrangement analyses were negative for both cases.
Conclusion: An atypical lymphoid infiltrate, including the one resembling lymphomatoid papulosis, associated with AFX has not been previously described. It is important to recognize the reactive nature of the infiltrate to avoid a misdiagnosis of lymphoma.

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Atypical fibroxanthoma (AFX) represents a cutaneous neoplasm that typically occurs on sun-damaged skin of elderly patients. It usually follows a non-metastatic course, presumably because of its superficial location, and is considered a superficial variant of pleomorphic sarcoma (formerly malignant fibrous histiocytoma[1]).

Microscopically, AFX is characterized by atypical spindled cells arranged haphazardly or in a vaguely fascicular pattern. The tumor cells may be multinucleated and may exhibit nuclear pleomorphism and frequent mitoses.[2] Several variants have been described, including spindled,[3] clear cell,[4–7] osteoid,[8] osteoclast-like giant cell,[9–12] chondroid,[9] pigmented,[13] granular cell[14–16] and myxoid types.[17]

Herein, we present two cases of AFX accompanied by a prominent lymphoid infiltrate containing atypical lymphocytes. One case possessed many CD30-positive atypical large mononuclear cells and thus mimicked lymphomatoid papulosis (LyP) or anaplastic large-cell lymphoma.

Case 1

A 91-year-old male with no previous history of skin cancer presented with a large, slightly exophytic growing lesion on the left parietal scalp for 6 months. The initial biopsy performed at an outside institution was interpreted as AFX. Two months later, the lesion had partially regressed, leaving a faintly pink and

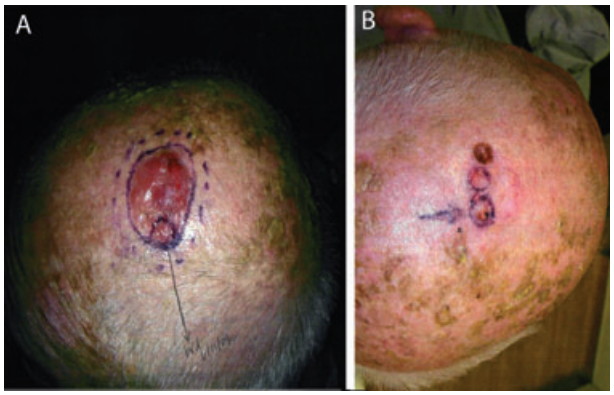

Fig. 1. Case 1: A) Recurrent atypical fibroxanthoma (AFX) arising on the left parietal scalp, measuring 2.8 × 3.5 cm. B) Clinical evidence of regression is observed adjacent to the tumor.

non-indurated plaque. On physical examination, a slightly elevated plaque measuring 2.8 × 3.5 cm was noted on the parietal scalp (Fig. 1). The lesion was re-excised and examined. No additional treatment was provided. After one and a half year follow up, he was free of disease with no evidence of recurrence or metastasis.

Case 2

A 68-year-old female had a lesion on the left thigh for 5 years. A partial biopsy was performed at an outside institution in 2007, and a 'reactive process' was favored. After a hip fracture, the patient noticed that the lesion became red and itchy with possible vesicles. She was otherwise healthy with no history of lymphoma or leukemia. On physical examination, there was a 1 cm tan to red nodule on her left thigh. A shave biopsy was performed.

Materials and methods

The available specimens for both cases were examined. Five micron sections were prepared from formalin-fixed, paraffin-embedded tissue blocks, and stained with hematoxylin and eosin for light microscopic examination. Immunohistochemical studies were conducted using monoclonal and polyclonal antibodies, including S-100 protein, melan-A, NKI-C3, cytokeratins AE1/AE3, CAM 5.2, high molecular weight cytokeratin K903, factor XIIIa, vimentin, smooth muscle actin, desmin, CD3, CD10, CD15, CD20, CD30, CD34, CD68 and ALK-1. Appropriate positive and negative controls were run in parallel with each immunohistochemical stain.

Both cases were evaluated for T-cell receptor gamma (*TCRγ*) gene rearrangement (GR), and case 1 was also evaluated for immunoglobulin heavy chain GR. Genomic DNA was extracted and amplified by multiplex polymerase chain reaction using two sets of primers: (i) 5′-fluorescent end-labeled primers that anneal to conserved sequences in the V and J regions of the *TCRγ* gene (TCRγGR) or the three conserved framework regions of the IGH gene (FR1, FR2 and FR3) (B-cell immunoglobulin heavy chain GR) and (ii) primers that target the human beta-globin gene. The amplified products were then subjected to fractionation using capillary electrophoresis followed by detection through differential fluorescence emission.

Results

Case 1 showed a large dermal malignant spindle cell neoplasm surrounded by a brisk and atypical lymphoid infiltrate (Fig. 2). The spindle cells had hyperchromatic and pleomorphic nuclei with a few multinucleated giant cells. As summarized in Table 1, immunohistochemically the tumor cells were strongly positive for vimentin and CD68, but were negative for S-100, melan-A, cytokeratin AE1/AE3, K903 and muscle-specific actin. A subset of the tumor cells was positive for CD10, but negative for all other lymphoid markers, including CD20. Procollagen, a marker that holds greater lineage specificity, was not available in our immunohistochemistry laboratory.[18] The surrounding lymphoid infiltrate consisted of a mixture of small to intermediate-sized CD3-positive T cells and CD20-positive B cells. Scattered CD30-positive large mononuclear cells (approximately ×2–3, the size of normal small lymphocytes), with dot-like golgi and membranous patterns were also present. The CD30-positive lymphocytes did not express ALK-1 or CD15. *TCRγ* gene and immunoglobulin heavy GR studies were negative. The findings supported a diagnosis of AFX with a reactive (lymphomatoid) lymphocytic host response. A repeat biopsy showed residual AFX with an adjacent loose fibromyxoid and fibrous stroma, the latter features correlating with the clinical impression of regression.

Case 2 showed a dermal-based atypical spindled and epithelioid cell proliferation with surface ulceration (Fig. 3). The tumor cells had pleomorphic nuclei with abundant eosinophilic cytoplasm. Scattered mitotic figures were present. Similar to case 1, the tumor was outlined by a brisk lymphoid infiltrate, but accompanied by conspicuous clusters of large lymphocytes and eosinophils. Immunostains (Table 1) showed that the tumor cells were strongly positive for CD10 and weakly positive for NKI-C3. There was focal and weak reactivity for smooth muscle actin and a very focal CD34 positivity. The tumor cells were negative for cytokeratins, S-100, factor XIIIa, desmin, CD3, CD20, CD30 and CD68. CD30 highlighted many large activated lymphocytes,

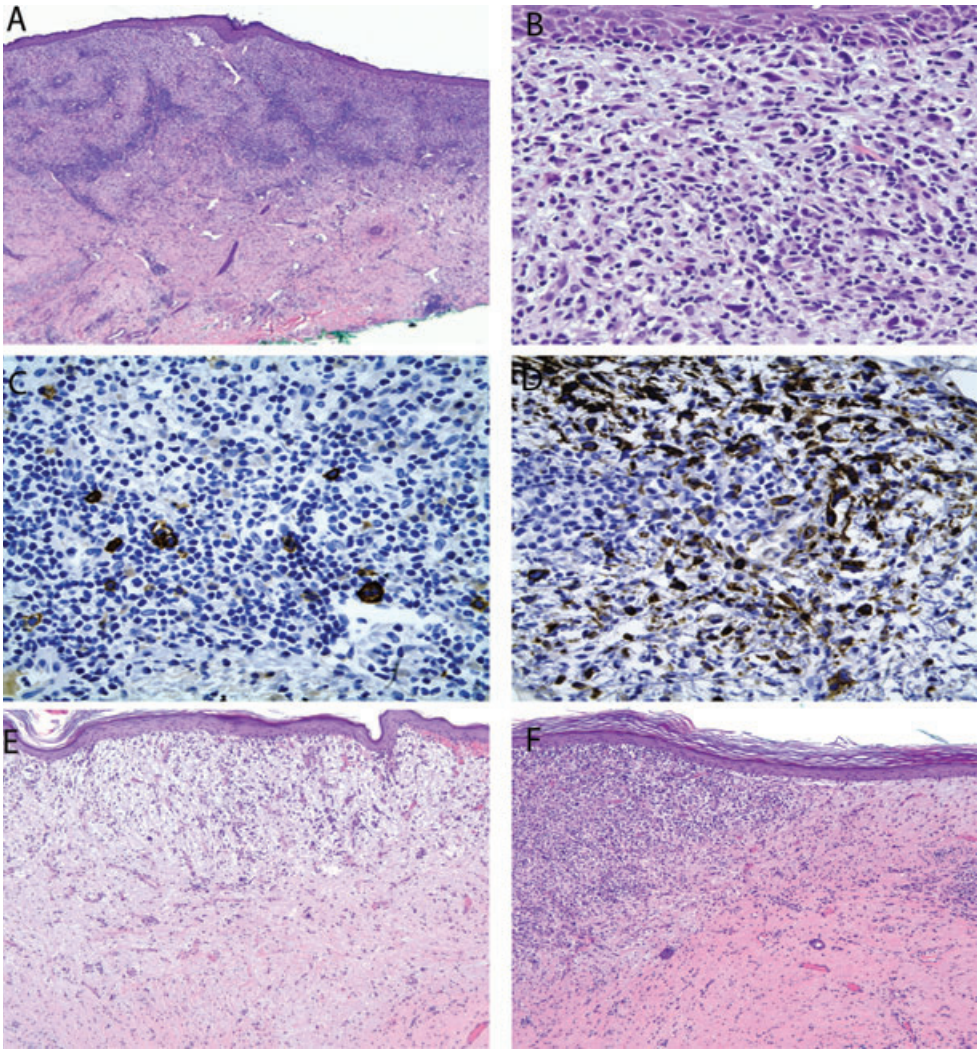

Fig. 2. Case 1: A) Tissue sections reveal a large dermal spindle cell neoplasm composed of atypical spindle cells haphazardly and in fascicles with interspersed multinucleated giant cells (H&E, ×40). B) The hyperchromatic and pleomorphic malignant spindle cells with rare multinucleated giant cells, surrounded by a brisk and atypical lymphoid infiltrate (H&E, ×400). C) A small subset of large atypical lymphoid cells that expressed CD30 (IHC, ×400). D) The spindled and pleomorphic tumor cells decorated with CD10 (×400). E) and F) Stromal regression is evident, adjacent to the atypical fibroxanthoma (AFX), corresponding to the clinical presentation in Fig. 1B; note in Fig. 2F the tumor in the upper left corner and regression on the right and below the tumor (H&E, ×100 each). H&E, hematoxylin and eosin stain; IHC, immunohistochemistry.

which did not react with ALK-1 or CD15. A *TCR*γ GR was negative for clonality. A diagnosis of superficial pleomorphic sarcoma compatible with AFX with an associated lymphomatoid response was rendered.

Discussion

AFX is presently considered a low-grade sarcoma[1] that has potential for local persistence[19,20] but rarely metastasizes.[21,22] AFX typically arises on sun-damaged skin of elderly patients but may rarely occur on other sites.[23,24] The histopathologic diagnosis of AFX can sometimes be challenging. The diagnosis of AFX is one of exclusion and requires the use of a panel of immunohistochemistry to rule out other cutaneous spindled malignancies, including sarcomatoid squamous cell carcinoma (SCC), spindle cell melanoma and leiomyosarcoma. For both of our cases, the immunophenotype of the tumor cells was consistent with AFX.

Interestingly, our examples of AFX elicited a robust lymphoid infiltrate with a variable density of atypical CD30-positive activated lymphocytes. One of our cases simulated LyP. CD15 and ALK-1 negativity suggested that systemic anaplastic large cell lymphoma or cutaneous Hodgkin's lymphoma was unlikely. We consider the possibility of a cutaneous CD30-positive lymphoproliferative disorder arising concurrently with AFX as a possible diagnosis. However, given the negative *TCR*γGR result, the lack of aberrant T-cell immunophenotype, the absence of a past history of a lymphoproliferative

Table 1. Immunostain results for the atypical spindled and pleomorphic tumor cells and the lymphoid infiltrate in the AFX cases

	Case 1		Case 2	
	Tumor cells	Lymphoid cells	Tumor cells	Lymphoid cells
S-100	–	NA	–	NA
Melan-A	–	NA	ND	NA
NKI-C3	ND	NA	+ (w)	NA
Factor XIIIa	ND	NA	–	NA
Smooth muscle actin	ND	NA	+ (w)	NA
Muscle-specific actin	–	NA	ND	NA
Desmin	ND	NA	–	NA
Vimentin	+	NA	ND	NA
Keratin cocktail	–	NA	–	NA
K903	–	NA	ND	NA
CD34	ND	NA	+ (f, w)	NA
CD68	+	NA	–	NA
CD10	+ (s)	–	+	–
CD20	–	+ (s)	–	+ (s)
CD3	–	+ (s)	–	+ (s)
CD15	–	–	–	–
CD30	–	+ (s*)	–	+ (s**)
ALK-1	–	–	–	–

NA, not applicable; ND, not done; f, focal; s, subset of cells (few*; many**); w, weak.

disorder and the lack of concomitant or subsequent clinical features compatible with lymphoma, a reactive (lymphomatoid) infiltrate associated with AFX was favored.

Spontaneous regression represents a known phenomenon associated with cutaneous tumors. It has been described with keratoacanthoma,[25–28] basal cell carcinoma,[29,30] Merkel cell carcinoma,[31] lymphoma,[32] halo nevus[28] and melanoma.[33] We suspect that the observation of a lymphomatoid infiltrate in our two AFX cases represents a regressive phenomenon. In fact, for case 1, there was evidence of regression following the initial biopsy. Recently, Stefanato et al.[34] reported a small series of patients with AFX showing microscopic features of regression, such as a variable amount of sclerotic collagen and lymphoplasmacytic infiltrates. However, they did not observe an atypical lymphoid infiltrate harboring large activated lymphocytes in their study. In contrast, we did not observe hyalinization or sclerosis in either patient's tumor. To our knowledge, this is the first report of AFX with regression characterized by an atypical lymphoid infiltrate containing prominent enlarged CD30-positive lymphocytes.

CD30 antigen is a 120-kDa transmembrane receptor that belongs to the tumor necrosis factor (TNF) superfamily and displays restricted expression in the

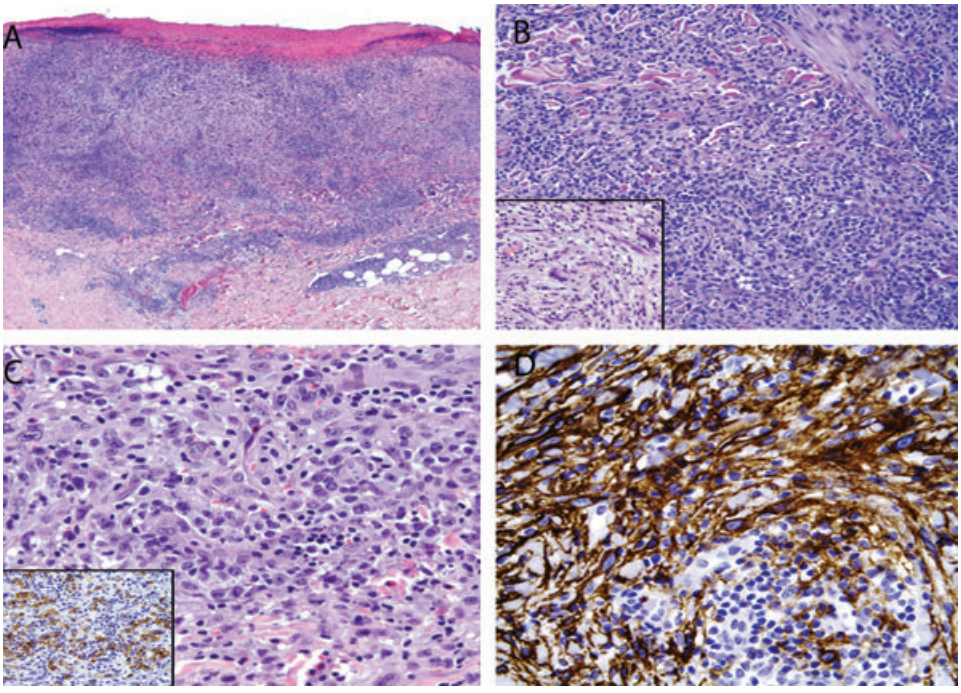

Fig. 3. Case 2: A) Tissue sections display epidermal ulceration overlying a dermal infiltrate of cytologically atypical spindled and multinucleated cells with abundant eosinophilic cytoplasm admixed with many lymphocytes and eosinophils (H&E, ×40). B) The tumor cells have abundant eosinophilic cytoplasm, with a surrounding infiltrate of lymphocytes and clusters of large lymphocytes (H&E, ×200; inset: H&E, ×400). C) The large atypical lymphoid cells are in close association with the malignant spindled and multinucleated cells and express CD30 (H&E, ×400; inset: IHC, ×400). D) The atypical spindled and multinucleated tumor cells label for CD10. (IHC, ×400). H&E, hematoxylin and eosin stain; IHC, immunohistochemistry.

subpopulations of activated T or B-lymphocytes.[35,36] The expression of CD30 antigen is the hallmark of a group of primary cutaneous CD30-positive T-cell lymphoproliferative disorders, including LyP and anaplastic large-cell lymphoma.[37,38] It can also be observed in cases of Hodgkin's lymphoma.[39] However, the presence of CD30-positive large cells is not unique to primary cutaneous CD30-positive lymphoproliferative disorders, and can be seen in a variety of reactive conditions, including arthropod bite reaction, viral infection or pityriasis lichenoides.[40] CD30-positive large lymphoid cells in these conditions are usually reactive T-lymphocytes and do not represent a lymphoproliferative process. Similarly, the presence of CD30-positive large lymphocytes in our AFX cases is considered a reactive phenomenon, given their intimate association with the tumor and resemblance to a lymphomatoid reaction. Similar observations have been reported in other non-melanocytic skin proliferations, including atypical squamous proliferations.[41,42] This phenomenon was first described in a case where multiple keratoacanthoma-like lesions arose in close proximity to classic lesions of LyP.[41] The authors postulated that the keratoacanthoma-like lesions represented a reactive change induced by atypical lymphocytes. Cespedes et al. described two cases of atypical CD30-positive lymphocytic proliferation in close association with keratoacanthoma and SCC.[42] The etiology is not well understood. Some authors suggest that the atypical lymphoid infiltrate is a direct cause of a secondary squamous proliferation as a result of lymphocytes producing cytokines, epidermal growth factor-like substances or other molecules that induce epidermal proliferation.[42] Other authors speculate that the CD30-positive lymphomatoid infiltrate may be a secondary reaction to squamous proliferation rather than the inciting primary event.[43,44] For our two AFX cases, we suspect that the lymphomatoid infiltrate is a secondary inflammatory response to the AFX and therefore may reflect early tumor regression. The phenomenon of an associated lymphomatoid reaction seems to be uncommon. In the reported large series of AFX, there is no mention of it.[2,20,45]

In summary, we present two cases of AFX associated with an atypical lymphomatoid infiltrate possessing enlarged CD30-positive lymphocytes. Clinicopathologic correlation supported interpretation as a lymphomatoid reaction to AFX, which we suspect represents a form of tumor regression. It is important to be aware of this phenomenon in order to prevent an erroneous diagnosis of cutaneous lymphoma and unnecessary anxiety and clinical workup for the patient.

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