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Case Reports

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Atypical Fibrous Histiocytoma and Atypical Fibroxanthoma: Presentation of Two Cases

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We report two rare examples of dermal fibrohistiocytic stromal tumors: one case of atypical fibrous histiocytoma (AFH) and another one of atypical fibroxanthoma (AFX), which can be confused in surgical pathology diagnosis with high-grade malignant neoplasm. Histologically, a proliferation of mononuclear, spindle-shaped, or histiocytoid cells and/or multinucleated cells, usually admixed with inflammatory cells was observed in both cases, but some clinicopathological differences allowed their distinction. Immunohistochemistry is of a little help in differential diagnosis between these two entities however, it is very useful in differentiating with other groups of tumors. Recognition of AFH and AFX is important, especially to prevent incorrect aggressive treatment in those cases that may be confused with high-grade sarcoma. Because of the potentially aggressive behavior in rare cases and the lack of clear-cut predictive morphologic patterns that would specify a poor clinical outcome, complete surgical excision in all cases is recommended.

Introduction

Fibrous histiocytoma (FH) is a common dermal lesion characterized histologically by a proliferation of mononuclear, spindle-shaped, or histiocytoid cells and/or multinucleated cells, usually admixed with inflammatory cells. Many clinicopathologic variants of FH have been described including aneurysmal, atypical, cellular, lipidized "ankle-type," palisading, and FH with osteoclast-like giant cells [5, 6, 14, 15]. Although considered to be benign neoplasms, certain variants of FH have been shown to have a tendency for recurrence locally after excision [1] or even rare metastases have been described [2]. One of these is atypical fibrous histiocytoma (AFH), infrequent, poorly documented lesion with only approximately 100 cases reported [3, 15]. Histologically, this tumor shows morphological features of classic FH, but with the presence of worrisome pleomorphic cells. Another skin lesion from the group of dermal stromal tumors, frequently confused with AFH is the atypical fibroxanthoma (AFX), previously referred to as pseudosarcoma of the skin [20], which is considered by most authorities to represent a superficial variant of malignant fibrous histiocytoma [19].

We report here two atypical fibrohistiocytic tumors: AFH and AFX with the emphasis on the similarity and differences in clinical and morphological presentation of these tumors. Their histopathological identification needs special attention in differentiating with high-grade soft tissue sarcoma.

Case Descriptions

Clinical presentation

Case 1: An 27-year old man with slightly elevated 1.6cm-diameter nodule on the thigh, which was completely excised.

Case 2: An 53-year old man presented with a 3.5cm-diameter polypoid nodule of the face in the temporal area which has been observed for more than 2 years. The tumor was excised with skin graft. One year later, patient is in good health with no history of recurrence.

Material and methods

In both cases, tissue was fixed in formalin and embedded in paraffin. Five-µm sections were cut from the paraffin blocks and stained with hematoxylin and eosin (H&E). For immunohistochemistry a *DAKO autostainer* automated staining system (DAKO Corporation, Carpinteria, CA, USA) has been used with antibodies listed in Table 1. Streptavidin-biotin-peroxidase (Histostan-SP kit, Zymed Laboratory's, San Francisco) was used and sections were stained with hematoxylin. The MIB-1 staining was assessed using computerized image analyzer Quantimet 600S (Leica).

Histopathology

Case 1. The excision specimen contained a well-defined skin nodule that compressed the overlying attenuated epider-

mis, which showed effacement of the rete ridges. The typical for FH grenz zone of papillary dermal sparing was present. This dermal nodule was composed of a population of pleomorphic spindled (fibroblast-like) and polygonal (histiocyte-like) cells, arranged focally in storiform pattern (Fig. 1A). The pleomorphic cells had large, hyperchromatic, and irregular (round to oval, cigar-shaped, or bizarre) nuclei with small, prominent nucleoli, and variable, often abundant, foamy or deeply eosinophilic cytoplasm having irregular and indistinct borders (Figs. 1C and D). Some of these cells with foamy cytoplasm contained hyperchromatic, bizarre two or less frequently, multiple nuclei (Fig. 1B, insert). Mitotic activity was low and ranged from 1 up to 2/10HPF. Atypical mitotic figures were not seen. Entrapment of collagen bundles was present. No necrosis was detected. The diagnosis of AFH was established.

Case 2. In this case polypoid symmetric nodule, well to moderately-well circumscribed, with collarette of squamous epithelium was present. Histologically, this tumor showed the presence of pleomorphic and/or spindle cells which were adjacent to the epidermis without an interposed grenz zone of papillary dermal sparing. Tumor did not extend into the subcutis and did not show necrosis however ulceration of the epidermis was noted. Superficially, there was a loose fascicular and haphazard array of cells with elongate, cigar-shaped nuclei (Figs. 2A and B). In deeper parts of the nodule tumor cells with higher degree of pleomorphism were observed bordered by a mononuclear inflammatory infiltrate. The mean mitotic rate was 9/10HPF (Fig. 2D), including atypical mitotic figures (Fig. 2, insert). Occasionally skin adnexa were found within the tumor, but they were not infiltrated. The morphology was consistent with AFX.

Immunohistochemistry

Both cases showed diffuse positivity for vimentin and focal positivity for SMA. There was no staining for keratin, S-100, CD68, and with HMB-45 antibody. These findings taken together with the overall morphologic features, are entirely consistent with a fibroblastic-myofibroblastic line of differentiation. Proliferation index paralleled the mitotic activity and MIB-1 was positive in 4.9% cells of AFH and 35% cells of AFX. The accumulation of p53 was found in AFX.

Discussion

The main purpose of this article is to characterize morphological spectrum of AFH and AFX with special emphasis on differential diagnosis and implications for treatment and prognosis. AFH usually presents on the extremities of young to middle-aged adults as a solitary, firm cutaneous nodule; however any anatomic site may be involved at any age [15]. In contrast, AFX typically presents on sun-damaged areas of the head and neck in elderly individuals as a polypoid, skin-colored or ulcerated nodule [10]. Histologically, AFH often causes confusion with AFX because in both tumors pleomorphic and/or spindle cells with bizarre nuclei and multinucleated cells are present. Additionally, the spectrum of morphologic features of AFH, especially the level of cytological atypia can be very wide, from small lesions with focal atypia set in the context of classic FH, to cases exhibiting marked pleomorphism, high mitotic index and infiltrative margins. Nonetheless, the morphologic differences exist [15].

AFX usually shows tumor cells that touch the epidermis without an interposed free grenz zone. AFX shows also no marked adjacent elastosis and associated classic features of FH (e.g., entrapped collagen bundles and epidermal hyperplasia). The pleomorphism of AFX is usually more diffuse than in AFH. AFX does not extend into the subcutis and usually does not show necrosis. The summary of main differences between AFH and AFX is presented in Table 2. Unfortunately, the immunohistochemistry is of a little help in differential diagnosis between these two entities, however it is very useful in differentiating with other groups of tumors. The differential diagnosis of AFH and AFX includes many entities listed below. Dermatofibrosarcoma protuberans can be distinguished from AFH and AFX by the absence of nuclear pleomorphism or presence of epidermal atrophy, and immunohistochemically by characteristic strong and

TABLE 1
Antibodies used for immunohistochemical studies

Antibody (clone)	Manufacturer	Dilution
CD34	Dako	1:50
CD68	Dako	1:50
S-100 protein	Dako	1:100
smooth muscle actin SMA	Dako	1:50
MIB-1 (Ki-67)	Dako	1:50
keratin KL-1	Dako	1:50
HMB-45	Dako	1:50
p53	Novocastra	1:50

TABLE 2
Main clinical and morphological features of AFH and AFX

Feature	AFH	AFX
age	young to middle aged	old
location	lower limb	head and neck
storiform pattern	yes	no
mitotic activity	medium to high	high
free grenz zone	yes	no
pleomorphism	focal to diffuse	diffuse
recurrence	rare	rare
metastasis	very rare	very rare

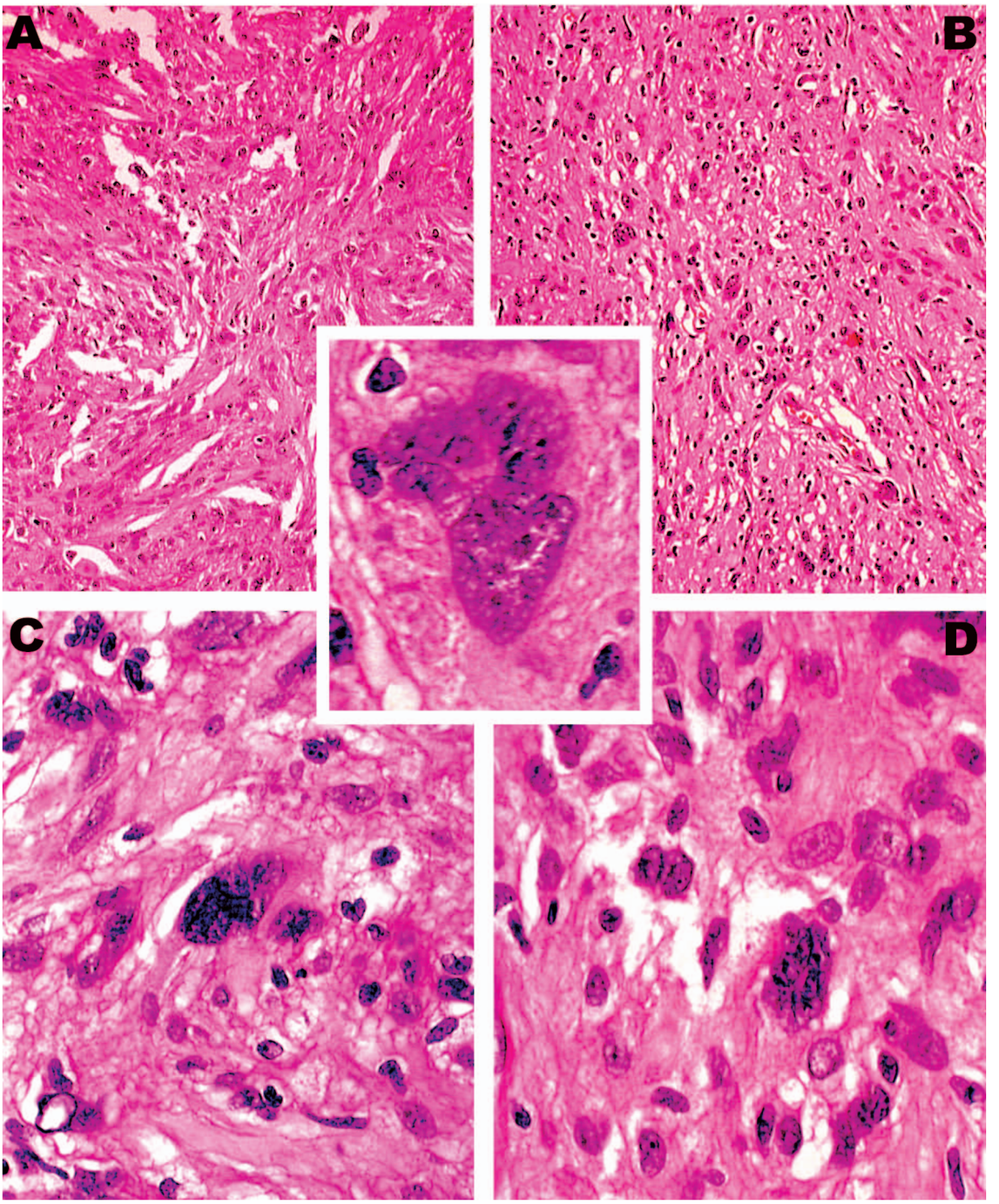

Fig. 1. Case 1: histology of AFH. HE. Typical storiform pattern (A, Magn. 100x) of spindle and polygonal cells (B, Magn. 100x). Some of them are pleomorphic, with large, hyperchromatic and irregular nuclei (C, D, Magn. 400x). Bizarre, multinucleated cell (insert, Magn. 400x).

diffuse positivity for CD34. Cutaneous leiomyosarcoma can be differentiated from AFH and AFX by the presence of intersecting fascicles of eosinophilic spindle cells with ovoid to cigar-shaped nuclei, demonstrating desmin positivity but no marked pleomorphism. Malignant melanoma and squamous cell carcinoma with spindle and pleomorphic cells can be distinguished from AFH and AFX by such morphologic features as epidermal origin and/or junctional activity and characteristic immunohistochemical staining with HMB-45 antibody and antibodies to cytokeratins, respectively. Angiosarcoma may occasionally exhibit marked pleomorphism; however, this tumor can be readily differentiated from

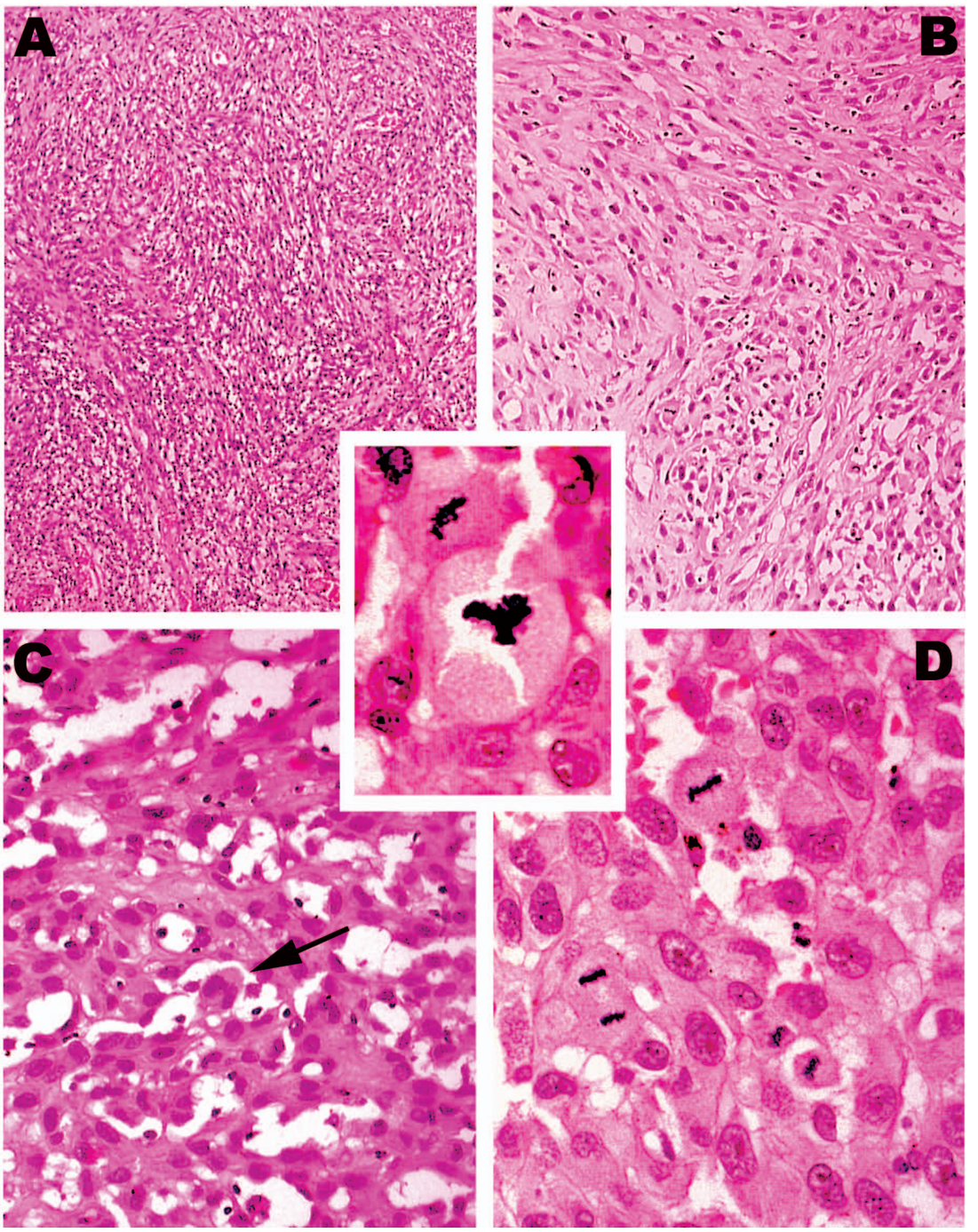

Fig. 2. Case 2: histology of AFX. HE. Diffuse arrangement of spindle and polygonal cells (A, Magn. 40x; B, Magn. 100x). Some of them are binucleated (C, Magn. 200x, arrow). High mitotic activity (D, Magn. 400x) with atypical mitotic figures (insert, Magn. 630x).

AFH and AFX because of typical vasoformative features. Malignant FH should also present no difficulties despite the opinion that AFX is superficial form of MFH. This neoplasm predominantly occurs as a more deeply seated, large, subcutaneous lesion composed of cellular mixture of storiform and pleomorphic areas of atypical cells. Most authors view AFH and AFX as a diagnosis of exclusion requiring a broad immunohistochemical panel to negate above mentioned diagnostic possibilities [8].

Kaddu et al. reported, that all cases of AFH which recurred were previously incompletely excised but recurrent tumors revealed no morphologic differences to those of the

primary lesions [15]. The same relation was observed in rare cases of AFH which metastasized; although no morphologic criteria were useful in prediction of such events. Previous cases of metastasizing AFH have been reported in young adults, with tumors located on the thigh and back, what is clinically rather not characteristic. The overall percentage of recurrent AFH is higher than in classical FH group (14% versus 1 - 2%) [4, 15]. Many authors agree that 3% of metastasizing cases of AFH is not a value, which would justify the term of low-grade sarcoma for this group [15]. Interestingly, AFX with its bizarre morphology, high mitotic index (including atypical mitoses), and nosological link to malignant fibrous histiocytoma has generally excellent prognosis after complete local excision, however exceptionally rare cases showing metastatic potential have been described [11, 12]. This information, common for AFH and AFX, is of great clinical importance because of possible overinterpretation of morphologic features as a sarcomatous proliferation and subsequently inappropriate therapy.

Little is known about pathogenesis of these two entities. AFH was considered previously as a inflammatory fibrohistiocytic process, but recently clonal chromosomal abnormalities in some of the FH variants, have been described which favors neoplastic origin [7, 18]. The tendency for recurrence and rare metastases of AFH argue also against a reactive lesion. Another hypothesis states, that AFH is a heterogeneous process, in which histiocytoid cells probably represent the neoplastic component and fibroblastic cells may represent a reactive proliferation or alternatively, it may represent a true neoplasm in which neoplastic cell type has been obscured by prominent reactive fibroblastic component [13]. p53 positivity seen in our AFX case is known to be a frequent finding, because it is observed in up to 86% of AFX [16, 17]. The central role for UV-related mutations of the p53 gene and subsequent development of this sun-exposed skin tumor has been also demonstrated [9].

In conclusion, AFH and AFX represent a peculiar and distinctive variants of locally aggressive, fibrohistiocytic neoplasms, that have a tendency to recur locally and a capacity to metastasize, although very rarely. Both lesions show sometimes worrisome pleomorphism. Distinction of AFH and AFX from high grade sarcoma is essential to prevent incorrect aggressive treatment. Because of the potentially aggressive behavior in rare cases and the lack of clear-cut predictive morphologic patterns that would indicate a poor clinical outcome, complete surgical excision is recommended [15].

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