Atypical fibroxanthoma: differential diagnosis from other sarcomatoid skin lesions

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Abstract

Atypical fibroxanthoma (AFX) is an uncommon cutaneous neoplasm that usually presents as a rapidly-growing nodule in sun-exposed sites in elderly patients. Despite its highly atypical histological appearance it is almost always associated with innocuous clinical behaviour. AFX is now generally regarded as the superficial counterpart of undifferentiated pleomorphic sarcoma (so-called malignant fibrous histiocytoma [MFH]). The former lesion is associated with an excellent prognosis in view of its small size, superficial location, and amenability to complete excision. Because a distinction between AFX and MFH requires assessment of the depth of invasion, a definitive diagnosis of AFX cannot be made on the basis of shallow biopsies. Other cutaneous tumours, including sarcomatoid squamous cell carcinoma (SCC) and spindle-cell melanoma, may have a histologic appearance that is indistinguishable from AFX on haematoxylin–eosin stained slides; immunochemical stains are therefore mandatory in the pathologic evaluation of such cases. There are no currently-known specific immunohistochemical markers (including CD10) which are diagnostic of AFX, and it remains a diagnosis of exclusion. Recent studies have highlighted the importance of other markers, such as high molecular-weight keratins (e.g., CK5/6, 34BE12, and MNF116) and p63 in the diagnosis of sarcomatoid squamous cell carcinoma; that tumour may fail to label for other keratin proteins. Recently, uncommon variants of AFX have been described that broaden its histological differential diagnosis.

Keywords atypical fibroxanthoma; carcinoma; diagnosis; differential diagnosis; melanoma; pathology; sarcoma; skin

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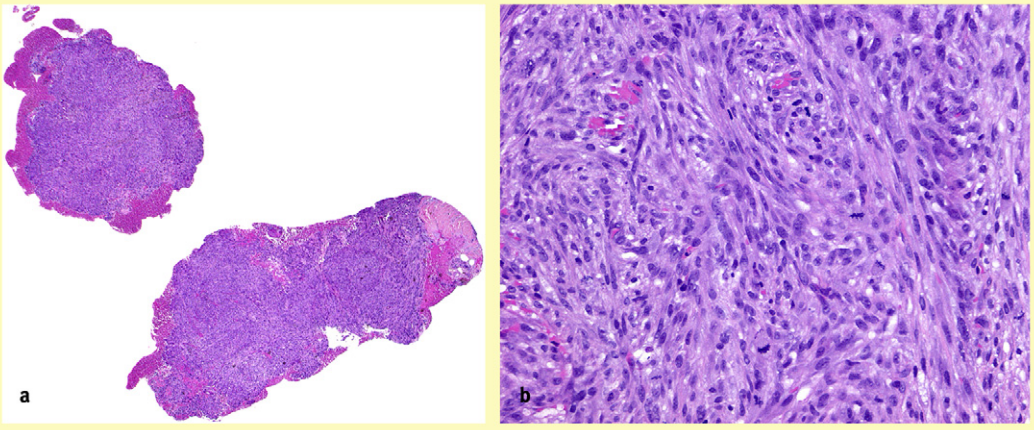
Atypical fibroxanthoma (AFX) is an uncommon cutaneous tumour that appears to be malignant histologically; however, it is paradoxically associated in most cases with favourable clinical behaviour.[1–5] Typically, this neoplasm occurs in elderly patients in severely sun-damaged skin, most commonly at sites that are exposed to intense sunlight, e.g., the head and neck and the upper limbs.[6] Early papers on the entity suggested that AFX could be diagnosed using its histologic features alone in haematoxylin–eosin (H–E) stained microscopic sections.[7] However, it is now well known that other malignant tumours, such as sarcomatoid squamous cell carcinoma and spindle-cell melanoma, among others, can be histologically indistinguishable from AFX; therefore, one must be certain to exclude such possibilities.[5,8–15,16,16a] Because AFX is, by definition, a superficial tumour, a definitive diagnosis requires complete excisional biopsy because the deep aspects of the tumour may not be present in other biopsy specimens. That is particularly true of superficial shave biopsies (Figure 1). If it is present, deep extension of the tumour would alter its diagnostic classification to that of undifferentiated pleomorphic sarcoma/"superficial malignant fibrous histiocytoma" (MFH). That is so providing that no definable cellular lineage of differentiation—such as epithelial, melanocytic, or myogenous—is demonstrable.

Histogenesis & pathogenesis of AFX

The term "atypical fibroxanthoma" was coined by Helwig in the early 1960s.[17] It was originally considered to represent a reactive condition rather than a neoplastic lesion, but that premise has since been discredited. In the decades after its original description, reports of "metastasizing AFX" appeared in the literature.[18–22] In many of those accounts, most of which appeared before the general use of immunohistochemistry, the diagnosis was made by morphological analysis alone. Furthermore, some of the cases showed vascular invasion, necrosis, and infiltration into subcutis or skeletal muscle; those features were not originally reported by Helwig. It is likely most of those tumours would now be reclassified as other lesions having a specific lineage of differentiation, with the benefit of adjunctive studies and application of more restrictive diagnostic criteria.

The histogenesis of AFX is controversial. Its immunophenotype suggests a combination of fibrohistiocytic (CD68-positive, actin-negative) and myofibroblastic (CD68-negative, actin-positive) constituents.[9,11,23] Ultrastructural studies of AFX have demonstrated cells with features of fibroblasts, myofibroblasts,



a & **b**. Atypical fibroxanthoma from the neck of a 75 year old male. A definitive diagnosis of AFX should not be made on cutaneous biopsies that do not excise the tumour (see text for details).

Figure 1

primitive mesenchymal cells, and transitional elements.[24] Whether AFX is a "dedifferentiated" form of another tumour, a lesion that arises *de novo* from a progenitor mesenchymal cell capable of multidirectional differentiation, or a family of closely related fibroblastic, myofibroblastic and fibrohistiocytic neoplastic entities is still unclear.[23]

Because AFX does not—by definition—show any evidence of epithelial, melanocytic or true myogenous differentiation, it has been categorized as a superficial cutaneous variant of undifferentiated pleomorphic sarcoma (so-called "malignant fibrous histiocytoma" [MFH]).[25] Nevertheless, it is possible that some examples of AFX represent clonally-evolved carcinomas (or other tumours) which have lost their immunophenotypic differentiation-related markers. However, we do not agree with the premise that ***all*** AFXs are sarcomatoid carcinomas, as recently posited. There is no dispositive evidence of epithelial differentiation in *bona fide* examples of AFX, at protein–chemical or ultrastructural levels of analysis.

The anatomic distribution, median patient age, association with other skin cancers, and ubiquitous evidence of chronic sun damage in the skin around AFX suggest a pathogenetic role for ultraviolet radiation in the development of this tumour. That notion is further supported by evidence from recent molecular studies showing DNA abnormalities that are considered to be markers of ultraviolet radiation-induced carcinogenesis.[26,27]

Terminology

As in many other areas of surgical pathology, there are some inconsistencies in dermatopathology regarding the terminology for cutaneous mesenchymal neoplasms. Despite its alarming histological appearance that suggests a malignancy, AFX is, in the vast majority of cases, associated with innocuous clinical behaviour. Hence, contextual use of the noun "fibroxanthoma" (denoting a benign neoplasm) appears reasonable. However, a histologically-identical tumour situated with its epicentre in the deeper soft tissue would be designated as undifferentiated pleomorphic sarcoma (MFH). In that instance, the indicated classification of the lesion is appropriate because of a distinct risk of metastasis. On the other hand, malignant cutaneous smooth muscle tumours are designated as leiomyosarcomas regardless of whether they are confined to the dermis or extend into the subcutis. As true of AFX, smooth muscle sarcomas that are contained within the dermis are associated with a very favourable clinical evolution.[28]

Many authors currently regard AFX as a superficial variant of MFH (pleomorphic undifferentiated sarcoma) because of their comparable histopathologic features and immunohistochemical profiles.[29–32] However, unlike MFH, AFX has an innocuous course. Therefore, clear diagnostic criteria are required to distinguish those two lesions. Prominent involvement of the subcutis was relatively common in early reports of AFX. In view of the documentation of metastasizing AFX in which the primary tumour showed prominent subcutaneous involvement, some authors have proposed a more restrictive definition of AFX to those tumours confined to the dermis (without subcutaneous extension) and absence of lymphovascular invasion, perineural infiltration, and tumour necrosis.[33] The advantage of adopting such a restrictive definition of AFX is that the predicted incidence of metastasis would be extremely low. Thus, we endorse this construct. However, not all authors agree on that point, and subcutaneous involvement by AFX has still been allowed in some recent series.[5]

Clinical features of AFX

AFX occurs mainly on sun-exposed skin, but potentially arises in virtually any cutaneous location.[6] It usually is observed in elderly patients, but some cases have been reported infrequently in young patients, including individuals who have xeroderma pigmentosum.[34,35] The clinicopathologic features of the latter lesions have differed from those of "classical" AFX, and it appears likely that the tumours in young people are probably variant forms of other neoplasms such as dermatofibroma. Most reports on AFX have not documented a sex preponderance, although some have suggested a greater frequency in males.[5]