

## Original Article

# Sixteen photogenic wonders from Down Under: a case series of Atypical Fibroxanthoma from Australia

## 源自澳洲的十六個精彩獵奇：澳洲的非典型纖維黃瘤病例系列

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Atypical Fibroxanthoma (AFX) is an uncommon skin tumour that typically follows a benign clinical course. Paradoxically, the histology may appear malignant. We present sixteen cases from Australia and important differential diagnoses including squamous cell carcinoma and cutaneous metastases of internal malignancy. Radiotherapy is an effective alternative to surgical excision for selected patients following adequate histological examination. Clinicians should suspect AFX in older patients presenting with a fast growing, solitary nodule on the head and neck. It is recommended that AFX be regarded as a reactive, localized tumour with a favourable prognosis after appropriate treatment in most cases. We propose the nomenclature of *Reactive Fibroxanthoma* to implicate chronic sun damage in the pathogenesis of this tumour.

非典型纖維黃瘤是一種較為罕見的皮膚腫瘤，一般臨床進展都表現為良性，但組織學上卻可反常地顯示為惡性。我們報告十六個澳洲的病例及其重要的鑑別診斷包括鱗狀細胞癌和內臟惡性腫瘤的皮膚轉移。除外科手術切除外，電療對經篩選而俱有充足組織學檢查的病者是另一可取療法。如年老患者在頭頸處有快速生長的單發結節，醫者須審視非典型纖維黃瘤的可能性。非典型纖維黃瘤應被視為一種反應性的局部腫瘤，大部份個案在接受合適治療後都有良好的預後。我們建議此腫瘤命名為反應性纖維黃瘤，以帶出其慢性陽光傷害的發病原因。

**Keywords:** Atypical fibroxanthoma, Australia, non-epithelial skin cancer, spindle-cell neoplasm

**關鍵詞：**非典型纖維黃瘤，澳洲，非上皮皮膚癌，梭形細胞腫瘤

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## Case series

Sixteen patients were identified by the senior author (SL) between September 2006 and February 2011. Atypical Fibroxanthoma (AFX) was diagnosed in each case by haematoxylin and eosin

(H&E) staining and immunohistochemical (IHC) staining of paraffin-embedded specimens. The clinical details, relevant history and management for each patient are summarized in Table 1. Four patient cases are outlined in detail below.

**Table 1.** Clinical details for sixteen patients with a final histological diagnosis of Atypical Fibroxanthoma

Case	Age/ Sex	Site	Size (mm)	Initial diagnosis	Relevant history	Management and outcome
1	82/M	Scalp	9 x 7	AFX	Surgery declined	Superficial Radiotherapy (10 Gray total)
2	78/F	Chest, upper	10 x 5	AFX	Lung cancer	Excision; deceased (unrelated cause)
3	75/M	Cheek, right	5 x 4	AFX	Previous BCC, right cheek; Radiotherapy to right cheek	Excision
4	90/M	Scalp	7 x 2	AFX	No significant history	Biopsy only; deceased (unrelated cause)
5	84/M	Scalp	17 x 18	AFX	Adjacent BCC	Excision
6	74/M	Scalp	27 x 20	SCC	Previous MFH	Excision; subsequent scalp SCC proximal to site of AFX
7	81/M	Scalp	5 x 3	AFX	Melanoma 15 years prior; BCC on left flank at presentation	Excision
8	81/M	Scalp	6 x 3	'Pseudoangio-sarcomatous' lesion	No significant history	Excision; final diagnosis AFX
9	80/M	Scalp	40 x 35	Clear-cell AFX	Previous NMSC; on warfarin	Excision; deceased (unrelated cause)
10	78/M	Earlobe, right	15 x 7	AFX	Previous NMSC	Excision
11	81/M	Scalp	20 x 18	Non-specific	Topical 5-fluorouracil treatment to the scalp prior to detection of AFX	Excision
12	81/M	Earlobe, left	14 x 10	AFX	No significant history	Excision
13	59/M	Forehead, right	12 x 6	AFX	No significant history	Excision
14	82/F	Nose	5 x 3	AFX	Greek heritage	Excision
15	82/M	Scalp	6 x 6	AFX	Low-dose prednisone ceased one year prior to diagnosis of AFX	Shave excision
16	83/M	Thigh, left	35 x 25	AFX	Previous NMSC	Excision

AFX=Atypical Fibroxanthoma; BCC=Basal Cell Carcinoma; SCC=Squamous Cell Carcinoma; NMSC=Non-melanoma skin cancer; M=Male; F=Female

**Case 1**

An 82-year-old male presented with a 9 x 7 mm lesion on his scalp. A diagnosis of AFX was based on IHC staining that was positive for CD10, and negative for cytokeratins and melanoma markers. The patient declined surgical excision for personal reasons; therefore, superficial radiotherapy was administered (2 Gy per fraction over 5 days). Treatment was effective and the patient has remained free of recurrence.

**Case 6**

A 76-year-old male presented with a 2 cm nodular lesion posterior to an excision site of an AFX that developed five years prior. Although the new lesion was thought clinically to be a resolving keratoacanthoma, H&E staining of the biopsy demonstrated features consistent with a squamous cell carcinoma (SCC). Wide local excision with split skin graft was performed to achieve complete tumour removal with clear margins. Subsequent analysis of this specimen revealed a poorly circumscribed spindle cell malignancy located in the dermis. IHC staining was negative for cytokeratin, S-100, and CD99, consistent with a diagnosis of AFX.

**Case 8**

A 79-year-old male patient presented with a 6 mm crusted, scalp lesion. The lesion was described as pseudoangiosarcomatous in appearance on biopsy, and the lesion was excised. IHC staining revealed positive staining for CD68 and CD10, weak positive staining for CD31, and negative staining for CD34 and Factor XIIIa, consistent with a diagnosis of AFX.

**Case 11**

An 81-year-old male presented with an anterior scalp lesion following topical 5-fluorouracil (5-FU) treatment for advanced actinic damage of the scalp. His background history included seborrheic dermatitis of the scalp that had recently been treated with appropriate topical therapy. An initial biopsy of the scalp lesion, which was performed following treatment failure with topical 5-FU, was non-specific. A second biopsy demonstrated

features suggestive of AFX, and subsequent wide-local excision confirmed the diagnosis of AFX. At time of follow-up, the treated area was clinically disease-free.

The mean age of the study cohort was 79.4 years (range 59 to 90 years). Fifteen Caucasian patients with Fitzpatrick type I-II and one non-Caucasian patient with Fitzpatrick type III skin each presented with a solitary nodule on sun-damaged skin. There were no recurrences or treatment complications reported by the thirteen patients who remained alive at the time of writing of this case series. The other three patients eventually died of causes unrelated to their skin tumours.

**Discussion**

Fifty years ago, Helwig coined the term "atypical fibroxanthoma" to describe a solitary, cutaneous nodule with histological features of an aggressive tumour that followed a benign clinical course.<sup>1</sup> Two years later, Bourne described 13 cases of "paradoxical fibrosarcoma of skin" in Australia.<sup>2</sup> These tumours had anaplastic microscopic features and yet evolved in a benign manner.

Epidemiological data on the prevalence of AFX is scarce. A recent survey of rare, non-melanoma, non-epithelial tumours identified AFX as the most frequent of 43 skin tumours reported. In this study, AFX occurred in one-third of cases, more than twice the rate as dermatofibrosarcoma protuberans, the next most common non-epithelial tumour identified.<sup>3</sup> In Australia, one hundred cases of AFX were reported from a single dermatopathology practice between 1996 and 1999.<sup>4</sup>

AFX typically presents as a rapidly growing, flesh-coloured or erythematous nodule, in chronically sun-damaged skin on the head and neck of an older patient (Figure 1). This tumour is usually solitary, may be ulcerated, and is rarely over three centimeters in diameter (Figures 2-4). AFX may also present as a slow-growing nodule on sun-

protected areas on the trunk and lower extremities (Figure 5), usually in younger patients.<sup>5</sup>

Our case series is consistent with previous reports that AFX occurs twice as often in males than females, and almost exclusively in Caucasian patients between 40 and 79 years of age.<sup>6,7</sup> However, as the patient of Greek heritage illustrates in case 14, AFX can also develop in non-Caucasian skin. Moreover, it should be noted that AFX can also occur on the external ear (Figure 1) and lower limbs (Figure 5). Our cases draw attention to the importance of thorough examination of all skin areas in fair-skinned patients, including acral body sites.

Variants of AFX include clear cell, osteoclastic giant cell, granular cell and pigmented AFX.<sup>8</sup> Our patient in case 7 presented with a clear-cell variant of AFX (Figure 6). Although metastases of AFX are exceedingly rare, we note a case report of peritoneal metastasis of clear-cell AFX.<sup>9</sup> There have also been reports of AFX metastasizing to lymph node, liver, peritoneum and lung, including two cases of perineural and intraneural invasion in Australia.<sup>10,11</sup> Recurrence rates between 5% and 7% have been reported, with tumours developing between three and 12 months following excision. However, these are most likely due to residual tumour regrowth rather than actual recurrence.<sup>12</sup> At the time of writing, the first patient recruited in



**Figure 1.** Atypical Fibroxanthoma (AFX) on the left earlobe.



**Figure 2.** AFX on the scalp with marked surrounding diffuse solar damage.



**Figure 3.** AFX on the scalp, clinically resembling a basal cell carcinoma.



**Figure 4.** AFX on the scalp with features simulating a seborrheic keratosis.



**Figure 5.** AFX on the left thigh.

September 2006 remains alive and well, with no recurrence and no new lesions.

### **Pathogenesis**

The pathogenesis of AFX has been suggested to be a reparative or reactive process developing as a result of chronic, cutaneous solar injury.<sup>13</sup> For over two decades, AFX has been considered an inflammatory reactive process associated with solar damage, irradiation, and/or previous trauma.<sup>14</sup> Mutations in the p53 tumour suppressor gene, which are common but not exclusive to UV-induced neoplasia, have recently been demonstrated in AFX.<sup>15</sup> In addition, previous reports of AFX in patients with internal malignancy have suggested that a defective host immune response due to malignancy or chemotherapy may also account for aberrant tumour behaviour.<sup>16</sup> Six patients in this series presented with a history of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC). One patient also had a past history of cutaneous melanoma.

Immune-deficiency or immune-suppression may be contributory in some patients. Indeed, multiple AFX have been reported in a subset of immunocompromised patients. A recent case of multiple AFX in a cardiac transplant patient on high-dose immunosuppression highlights the



**Figure 6.** AFX on the scalp; clear-cell variant. Patient had been on anti-coagulation therapy.

need to consider AFX for rapidly-growing tumours in this sub-group of patients.<sup>17</sup> Due to the acknowledged importance of solar irradiation in its pathogenesis, and rising evidence of a contributing role of immune suppression, the term "atypical" seems ambiguous and confounding. Indeed, our sixteen cases appear more typical than atypical in nature, given our current understanding of this tumour. All tumours have appeared on body sites of older patients exposed to extensive solar irradiation.

So what's in a name? The unfortunately ubiquitous misnomer, 'Hutchinson's Melanotic Freckle' clearly highlights the risks of a pervasive and misleading name. This malignant tumor, now known as 'Lentigo Maligna' is certainly not benign, as its outmoded name suggested. Consequently, we would like to introduce the novel and meaningful nosology, "*Reactive Fibroxanthoma*" to more accurately reflect our current understanding of the pathogenesis of AFX as a reactive proliferation of spindle cells, most commonly due to a photogenic insult. By doing so, we hope to generate further research interests and refocus clinical attention on this photogenic wonder.

### **Histopathology**

AFX presents as an unencapsulated dermal

tumour, composed of large, spindle-shaped cells arranged in a haphazard fashion (Figure 7). Saucerization biopsy – that is, wide shave biopsy – is an alternative sampling technique that permits evaluation of the dermal-epidermal junction, including peripheral edges of the lesion, where there may be diagnostic clues. This technique is useful to distinguish squamous cell carcinoma (SCC) or in-situ melanoma, but prevents histological assessment of tumour depth.

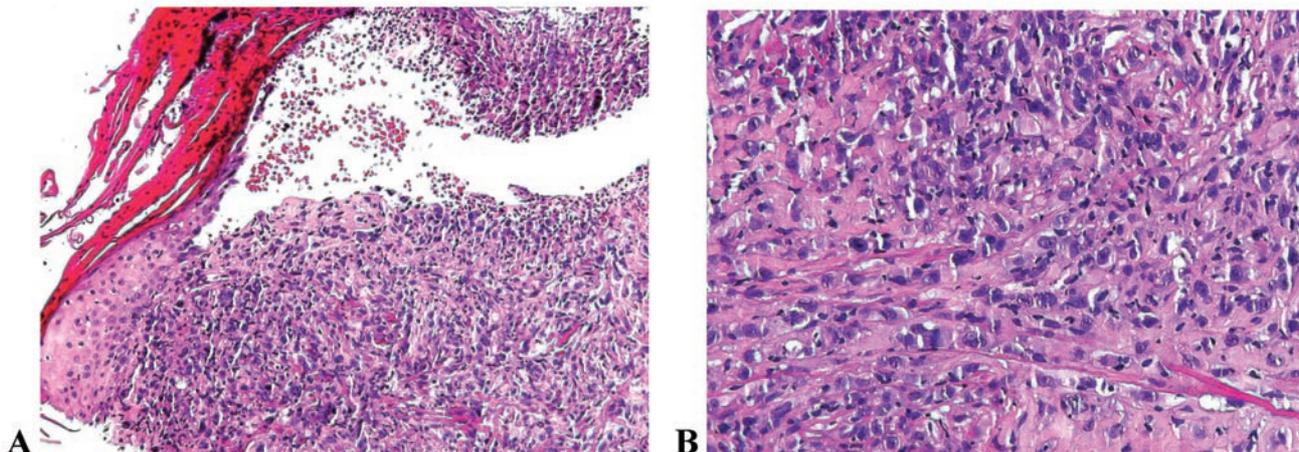
The principle of diagnosing AFX remains one of exclusion: a negative IHC staining for melanoma marker S-100 protein and the epithelial protein keratin form the cornerstone of histological diagnosis. However, IHC staining of AFX may be variable because tumour antigens are unpredictably expressed, presumably due to the primitive and pleomorphic nature of the relevant cells. Our series emphasizes the difficulty in distinguishing these lesions from other common cutaneous tumours. One lesion (case 6) was initially described as a resolving keratoacanthoma on clinical inspection, but H&E staining of the biopsy sample demonstrated features of an SCC. Subsequent histological examination of the excised lesion revealed a poorly-circumscribed, spindle cell dermal tumour. IHC staining was negative for cytokeratin, S-100 and CD99, confirming the final diagnosis of AFX.

### Differential diagnoses

Clinical differential diagnoses of AFX are listed in Table 2. Cutaneous SCC is the most common non-melanoma skin cancer of the head and neck. While SCC is a malignant tumour of keratinocytes arising within the stratified squamous epithelium, AFX is a non-epithelial, dermal tumour.<sup>18</sup> The distinction between poorly differentiated SCC and

**Table 2.** Clinical differential diagnoses of Atypical Fibroxanthoma

Epithelial cell origin	
	Squamous cell carcinoma (SCC)
	Basal cell carcinoma (BCC)
	Keratoacanthoma (KA)
Non-epithelial cell origin	
	Dermatofibrosarcoma protuberans
	Malignant fibrous histiocytoma (MFH)
	Merkel cell carcinoma
	Leiomyosarcoma
	Angiosarcoma
Melanoma	
	Nodular melanoma
	Desmoplastic melanoma
	Amelanotic malignant melanoma
Other	
	Cutaneous metastases of internal malignancy
	Kaposi's Sarcoma
	Seborrheic Keratosis



**Figure 7.** Atypical Fibroxanthoma, Case 7. (A) The tumour is dermal based, and does not involve the overlying epidermis (H&E stain, 100x). (B) The tumour is composed of pleomorphic, spindle and epithelioid cells which are mitotically active (H&E stain, 400x).

AFX can be difficult on histology alone. Key features favouring SCC include involvement of the overlying epidermis and an epithelial architectural pattern, often limited to the superficial portion of the tumour. Possible pitfalls in diagnosing AFX by H&E alone include lack of sampling of the junctional component of an ulcerated or fragmented specimen, and pseudo-epitheliomatous squamous hyperplasia that may supervene following a biopsy.

AFX parallels KA as a controversial tumour that is often mistaken for SCC. KA has been regarded as a well-differentiated form of SCC that commonly presents on the head and neck and may spontaneously resolve.<sup>19</sup> While clinical similarities between KA and primary SCC justify surgical excision with adequate margins, superficial radiotherapy has been demonstrated as an effective treatment option in selected patients presenting with KA and well-differentiated SCC.<sup>20</sup> Cutaneous metastasis of internal malignancy continues to be an occult problem that may be overlooked in the differential diagnosis of head and neck tumours. In a large meta-analysis of 20,000 cancer patients, the incidence of cutaneous metastases on the neck, scalp, and face was 11%, 7%, and 5%, respectively.<sup>21</sup>

Malignant fibrous histiocytoma (MFH), the most common malignant soft tissue tumour, may be distinguished from AFX by its depth of involvement and necrosis.<sup>22</sup> Merkel cell carcinoma, an aggressive neuroendocrine cutaneous neoplasm, also presents on sun-damaged skin of older people.<sup>23</sup> Amelanotic melanoma has distinctive cellular nesting pattern on histology, as well as IHC stains of melanin, and electron microscopic features of melanocytic organelles and/or pigment.<sup>24</sup> Classic Kaposi's sarcoma (KS) commonly presents in older males as firm, purple nodules, which may be difficult to distinguish from pigmented AFX.<sup>25</sup>

### **Treatment**

It has generally been accepted that the first line treatment of AFX is local surgical excision down

to subcutaneous tissue,<sup>26</sup> with superficial radiotherapy as a useful adjunct. Superficial radiotherapy is recognized as an important treatment modality for non-melanoma skin cancers in Australia. Other lesions such as plantar warts, classic KS, and lentigo maligna, have also been successfully treated with radiotherapy.<sup>27,28</sup> Although no clear effectiveness data currently exist for radiotherapy as treatment of AFX, response rates are likely to be similar to cutaneous SCC: rates over 90% are reported in tumours less than three centimetres in diameter.<sup>29</sup> Superficial radiotherapy may offer an effective therapeutic adjunct for AFX in a subset of older patients who are unable to undergo surgery. However, at present, no clinical treatment guidelines exist. Evidence-based recommendations of optimal treatment margins and duration of follow-up are keenly awaited.

Most dermatologists agree that chronic sun exposure plays a key role in the pathogenesis of AFX. Accordingly, it is curious and a wonder that they are usually solitary rather than multiple, as is the case with solar keratoses. In light of the current understanding of the pathogenesis of AFX as a reparative process, we propose the alternative nomenclature of *Reactive Fibroxanthoma* to incorporate the pathogenic role of solar radiation and defective immunity. After half a century of being under-exposed, we feel that this skin tumour deserves a new name and a fresh look!

### **Conclusion**

While relatively rare, AFX remains an important skin tumour in a sun-drenched country such as Australia. Under-diagnosis and at times excessive treatment of this tumour are of concern in dermatology, cancer medicine and general practice. Excision is the treatment of choice and radiotherapy is an effective treatment option for selected patients. There is a need for further studies to provide epidemiological data that will underpin the development of clinical treatment guidelines. In addition, this case series demonstrates the

'typical' nature of these lesions, in stark contrast to its confounding name. The suggested nomenclature of *Reactive Fibroxanthoma* may focus more enlighteningly on the reparative process underlying this skin tumour and eliminates the ambiguous prefix 'atypical' from contemporary nosology.

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