



## A Case of Atypical Fibroxanthoma. Barriers to Diagnosis and Literature Review

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### Abstract

**Introduction:** Atypical fibroxanthoma is a low grade soft tissue sarcoma infiltrating the dermis containing pleomorphic spindle cells. Pleomorphic dermal sarcoma is a rare dermal tumour on the same morphological spectrum as atypical fibroxanthoma, with greater potential for malignancy. Distinguishing between the two tumours can have a significant impact on management.

**Case:** An 81-year-old gentleman presents with a black haemorrhagic lesion demonstrating features of atypical fibroxanthoma. The diagnostic pathway of this case is followed, focusing on wide local excision and histopathological examination of the offensive tissue, and highlighting decisions made during these stages.

**Discussion:** Common clinical features of atypical fibroxanthoma is detailed, and potential for larger trials to focus on clinical features in symptomatic individuals. The difficulty orientating auricular tissue and methods to reduce potential loss of tissue is discussed. Finally, this report delves into guidelines for wide local excision and what is appropriate for atypical fibroxanthoma or pleomorphic dermal sarcomas.

**Conclusion:** Management of atypical fibroxanthoma can vary from pleomorphic dermal sarcoma or more aggressive sarcomas. This report emphasises the need for a streamlined diagnostic pathway to improve treatment benefit for patients and reduce waiting times.

**Keywords:** Malignant Fibrous Histiocytoma (MFH); Undifferentiated Pleomorphic Sarcoma (UPS); Pleomorphic Dermal Sarcoma (PDS)

### Introduction

In 1963 cutaneous mesenchymal tumours arising from bone or connective soft tissue with spindle, and histoid cells were originally described by Margaret R. Murray as Malignant Fibrous Histiocytoma (MFH) [1]. In 2002 the classification was changed to Undifferentiated Pleomorphic Sarcoma (UPS) as it described a soft tissue tumour of greater recurrence and metastasis in comparison to clinically similar Atypical Fibroxanthomas (AFX) [1]. As further examples of UPS were identified it became necessary to

differentiate subtypes of pleomorphic sarcoma by location of origin. This led to the term Pleomorphic Dermal Sarcoma (PDS) being proposed by Dr Christopher Fletcher to subcategorise UPS that develops in the dermis and invades into the subcutis compared to UPS that may occur in internal or retroperitoneal organs [2]. As the term PDS became common nomenclature it was adopted in a later addition of the WHO classification of soft tissue tumours in 2013 [2]. AFX and PDS are often considered to be neoplasia of the same origin, along a spectrum of progression [2]. AFX was first

acknowledged by Helwig during the 1960's, characterising a tumour of fibroblastic origin with a clearly circumscribed infiltration of the dermis by pleomorphic spindle cells and polynuclear atypical giant cells undergoing mitoses [2]. Despite the histomorphology of AFX and PDS being similar, a diagnosis of PDS is confirmed by subcutis spread, areas of necrosis and perineural or lymphatic spread [2].

The majority of AFX and PDS cases occur in elderly males [3]. When patients first present with AFX or PDS, the tumours are often found in areas regularly damaged by sunlight or exposed to radiation by other means [2]. These tumours do not have a characteristic appearance but are often observed as ulcerated nodules of flesh colour that do not grow beyond a few centimetres in size [2,4]. The greatest frequency of patients that develop AFX or PDS are in their 70's or 80's, however cases have been identified in younger patients with immunosuppression or a genetic damage to tumour suppressor genes [2]. Current evidence demonstrates an 8.8%-20% metastasis rate in PDS compared to AFX which only has a 1-2% chance of metastasis post excision [2]. Similar statistics are reflected in the recurrence rate of 17-35% in PDS, whilst AFX recurs 4.6% to 11.3% of the time [5].

Management of AFX and PDS can vary due to the rate of progression in PDS being greater than AFX. Excision of AFX tumours can often lead to a cure in the patient's condition, whilst PDS often has a greater rate of recurrence due to the nature of PDS having infiltrated into lymphovascular or perineural tissue. PDS management initially involves excision with wide margins as in AFX so that the sample can undergo appropriate histological investigation. Once the diagnosis of PDS is confirmed, further management is dependent on whether the resection margins are positive or not and can include adjuvant radiotherapy [5].

Immunohistochemistry is used in the diagnostic process of AFX/PDS to rule out other tumours including melanoma, cutaneous small cell cancer, vascular tumours, or other sarcomas [2]. When performing an immunohistochemistry panel to exclude other diagnoses there should be a minimum of two cytokeratin (AE1/3, MNF116, KL1, or CAM5.2), two melanocytic markers (S100, Sox10) and a muscle marker (desmin) [2]. Additional markers such as CD10, CD34, ERG, alpha smooth muscle actin can also be added to the panel for a more conclusive diagnosis [2]. Most AFX/PDS tumours will be positive for CD10 but can also indicate a positive result for CD99 and procollagen-1 [2].

AFX and PDS both require a high mutation load (42.7 mutations per mega base in PDS) with most genetic changes being in TP53-loss-of-function mutations, present in all cases of AFX/PDS [2]. Genetic mutations have also been identified in DNHD1, RTN1, ZBTB8A, NCKAP5L, FAM200A, NOTCH1/2, FAT1, RTL1, TRAPP12 and GNAS [2].

## Case

An 81-year-old Caucasian male visited the accident and emergency department due to a black haemorrhagic lesion on the left auricle over the head of the helix. The lesion had bled on contact over the course of three weeks causing concern for the patient who is notably on warfarin. The patient had no additional symptoms with the lesion, which was well-circumscribed, scabbed over, immobile, 15 mm x 7mm in size and oblong in shape. On review of the patient's family history, past medical and surgical history there was no specific cause for the presence of the lesion. The patient was promptly referred to ENT clinic, leading to the patient being placed on a 2-week wait pathway to have the lesion excised and investigated further. Initial investigation of urinalysis, blood tests, liver function test, chest x-ray and head CT did not reveal any relevant findings. The patient underwent a wedge excisional biopsy of the left middle helix under local anaesthetic with a 5 mm safety margin. Macroscopy revealed a 15 x 15 x 12 mm haemorrhagic piece of tissue with a cream-white homogenous appearance along the cut surface. A few weeks later the histopathology report returned describing a polypoid piece of ulcerated skin showing a highly vascularised spindle-cell neoplasm composed of sheets and fascicles of highly pleomorphic cells. These cells displayed plump, irregular nuclei and multinucleated cells undergoing frequent atypical mitoses, however it was noted that no necrosis was seen in the tissue. Due to an issue in orientation when embedding the excision, the base of the lesion was lost. This precluded the histopathologist from commenting on whether an infiltrative growth was present or not, as well as the depth of invasion and the presence/ absence of perineural or lymphovascular invasion.

Immunohistochemistry revealed tumour cells that are positive for CD10 and negative for CD31, CD68, S100, MelanA, HMB5, AE1/AE3, MNF116, CK 5/6, EMA, p63, D240, CD34, CD117, SMA, Desmin and CD56. After receiving the result of microscopy and immunohistochemistry a multidisciplinary team of clinicians determined that complete excision would be necessary to

distinguish between AFX and PDS. The patient was booked for an additional excision of the area surrounding the previously excised lesion and two tissue samples were removed.

The second excision was negative for any residual sarcoma tissue, confirming the diagnosis of AFX with no further neoplasia, rendering chemotherapy or adjuvant radiotherapy superfluous at this stage. The patient was discharged from ENT clinic.

## Discussion

Atypical fibroxanthomas is a neoplasm originating from mesenchymal progenitor cells, with a moderate potential for malignancy, being classified as a low-grade tumour [6]. Even amongst skin cancers AFX is rare, making up approximately 0.2% of all malignant skin cancers, limiting further research [7]. On examination, AFX often appears as either red plaque or nodule with central ulceration or crusting [6]. AFX is commonly found to be symptomatic, with patients attending to find out the cause of the lesion, however in this case report the patient attended with frequent episodes of bleeding from a black ulcerated lesion. This case study aims to highlight the importance of symptoms and clinical features when trying to confirm or rule out cases of AFX. This is necessary as the tumours can enlarge rapidly up to 2 cm, increasing the risk of further invasion into perineural or lymph vascular tissue. Pathogenesis of AFX is agreed to heavily involve UV damage [2]. This is supported by a greater frequency of AFX cases being present in the head and neck regions, which are more easily exposed to sunlight [6]. Mutations of p53 at dipyrimidine sites are found in AFX as well as other types of skin tumours supporting occurrence due to UV [2,8].

During the diagnostic process of this case report there was a delay in diagnosis of AFX as the histopathologist noted that the base was lost during embedding, preventing confirmation of AFX or PDS. When embedding skin biopsies, tissue orientation is key for a complete representation of the tissue in question, however multiple issues arise in the case of ear tissue [9]. Auricular tissue can be irregular in shape compared to wedge biopsies from other areas of skin and processing the tissue can cause it to become further distorted [9]. This makes embedding difficult but is often mitigated through colour coding or dotting of tissue borders so the area of interest can be identified, however this is not common practice in all laboratories [9]. Further research would be beneficial

to determine the impact on colour coding and dotting on reduction of incidents in embedding. Another concern would have been the mistaken use of adjuvant radiotherapy in this patient, whilst awaiting the microscopy result for the second biopsy. Fortunately, it was decided by MDT that the patient did not require additional management in this case and the second biopsy of the wider margin excluded additional neoplasia.

Another consideration for diagnosis and management of AFX is whether to use Mohs microscopic surgery (MMS) or wide local excision (WLE) when removing the lesion, both of which are accepted methods according to latest guidance [10]. A systematic review of surgical excision margins for AFX and UPS identified 101 AFX tumours in 99 patients affirming a preference for MMS over WLE in the literature [10]. The difficulty with MMS is the limited availability of facilities with the capacity to perform the procedure and adequate number of laboratory personnel to support it. Therefore, the systematic review aimed to determine acceptable uniform margins for WLE of AFX [10]. The conclusion was margins of 1 cm for tumours 1-2 cm in size and 2 cm for AFX greater than 2 cm in size preoperatively [10]. In this case, excisional biopsy was performed with a 5 mm wide margin, therefore an additional excision was necessary for a conclusive diagnosis.

## Conclusion

It is important to have a greater understanding of AFX and its more aggressive cousins PDS and MFH as the management pathway can differ between simply removing the tissue to supplying adjuvant radiotherapy and chemotherapy. This case highlights the unusual clinical presentation of a case of AFX, noting the potential for comparing symptomatic and asymptomatic cases of AFX. Rapid diagnosis of skin tumours is a necessity to rule out more aggressive neoplasms. Areas of diagnosis delay were highlighted in this case when assessing the tissue sample and determining excision margins for this case. Solutions offered to reduce the risk of complication tackled the stage of embedding irregular auricular tissue and whether safety margins for WLE were appropriate in this case. Ultimately this case report analyses the diagnostic pathway for a rare middle grade tumour and some of the barriers for a conclusive diagnosis.

## Conflicts of Interest

The Authors declare no conflict of interest.

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