Pleomorphic dermal sarcoma in a man with HIV: report with next-generation sequencing analysis and review of the atypical fibroxanthoma/pleomorphic dermal sarcoma spectrum

Stella X Chen*[1], Dawn Z Eichenfield*[2], Charisse Orme[2], Brian Hinds[2]

*Authors contributed equally

Affiliations: [1]University of California San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA, USA, [2]University of California San Diego Department of Dermatology, 8899 University Center Lane, Suite 350, San Diego, CA, USA

Corresponding Authors: Stella X Chen, 9500 Gilman Drive, La Jolla, CA 92093, Email: stella.x.chen@gmail.com; Dawn Z Eichenfield, 8899 University Center Lane, Suite 350, San Diego, CA 92122, Email: Dawn@eichenfield.com

Abstract

Atypical fibroxanthoma (AFX) is a rare cutaneous fibrohistiocytic tumor that typically arises on chronically sun-damaged skin, such as the head and neck, as a nondescript ulcerated papule, nodule, or tumor. The clinical prognosis is usually favorable and metastasis is rare. Pleomorphic dermal sarcoma (PDS), or undifferentiated pleomorphic sarcoma, is a recently introduced diagnostic moniker for AFX-like tumors with more aggressive clinical and histologic features such as necrosis and vascular invasion. The exact relationship between AFX and PDS has been debated. Diagnosis of these tumors is generally based on immunohistochemical staining to exclude other mimics. A wholly specific marker for this tumor does not exist, leading to diagnostic ambiguity in certain cases. Herein, we present a case of pleomorphic dermal sarcoma in a 53-year-old man with human immunodeficiency virus that displayed patchy S100 staining concerning for melanoma upon hospital pathology review. Next-generation sequencing analysis confirmed a mutation pattern consistent with published molecular signatures of AFX/PDS. In discussing this case, we review the current understanding of AFX/PDS and discuss diagnostic pitfalls, as well as emphasize on how next-generation sequencing techniques might improve accuracy in the diagnosis of tumors in the spectrum of AFX/PDS.

Keywords: atypical fibroxanthoma, malignant fibrous histiocytoma, pleomorphic dermal sarcoma, undifferentiated pleomorphic sarcoma, de-differentiated melanoma, immunosuppression, HIV, deep sequencing.

Introduction

Atypical fibroxanthoma (AFX), first described by Helwig, represents a low-grade intradermal sarcoma of fibrohistiocytic lineage, often situated on the head/neck of elderly Caucasian men [1, 2]. The clinical prognosis is typically favorable with rare reports of metastasis. Although data remain scarce, the estimated recurrence and metastatic risks in AFX are less than 5% with clear surgical margins, whereas the published recurrence/metastatic risks of pleomorphic dermal sarcomas (PDS) can be as high as 20% [3–5]. In immunocompetent individuals, the rate of AFX metastasis is 2.75% and the recurrence rate for wide local excision (WLE) is 7.6% [6, 7]. In immunosuppressed individuals, publications have described higher rates of recurrence (25%) and metastasis (8%), [8]. In these individuals, the recurrence rate after WLE can be upwards of 60% [8].

There is uncertainty as to the exact percentage risk for progression of AFX/PDS. Subcutaneous

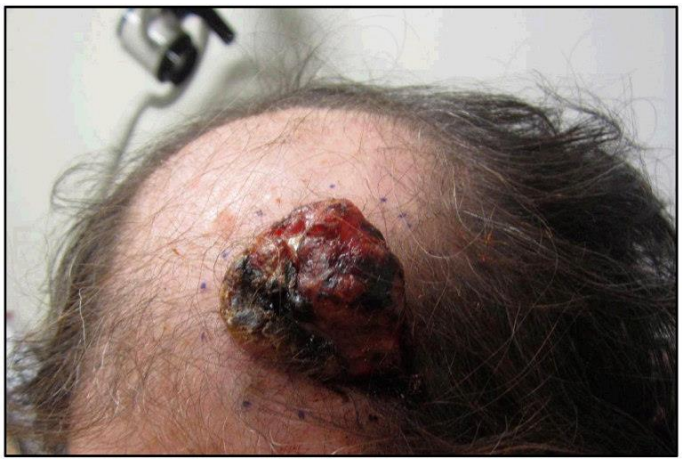

Figure 1. *A four-centimeter exophytic, bleeding mass enlarging for eight months on the scalp of a 53-year-old man.*

extension and vascular invasion are well-accepted attributes of PDS, diverging from the favorable prognosis of AFX [9]. As expected with other non-melanoma cutaneous malignancies, immunosuppressed individuals are more vulnerable to disease progression, including recurrence and metastasis, which may inflate standard risk assessment in AFX cohorts [5, 10]. Herein, we describe a polypoid scalp tumor with nodal metastasis in the setting of human immunodeficiency virus (HIV) and expand on pitfalls in the diagnostic workup. We review our current understanding of the AFX/PDS spectrum and discuss how sequencing technologies can contribute to accurate diagnoses.

Case Synopsis

A 53-year-old man with history of HIV (CD4 count: 242/millimeter^3, viral titer: 242 copies/milliliter), non-melanoma skin cancer (NMSC), and anal cancer presented to our hospital with a four-centimeter exophytic, bleeding mass on his scalp, enlarging for eight months (**Figure 1**). Histopathologic examination revealed an atypical pan-dermal, polypoid proliferation of pleomorphic cells with multinucleate forms and widespread mitotic figures (**Figure 2A**, **B)**. CD10 immunostaining showed strong expression; p63, SOX-10, ERG, and desmin were negative, consistent with a provisional diagnosis of hemorrhagic atypical fibroxanthoma/pleomorphic dermal sarcoma (AFX/PDS), (**Figure 3**). However, patchy S100 immunostaining was also observed and a diagnosis of melanoma was rendered in the hospital laboratory (**Figure 2C)**. S100 staining was patchy as opposed to diffuse and co-localized consistently with interstitial dendritic cells and Schwann cells (**Figure 2C)**. To best classify the tumor and bolster the diagnosis, massive parallel sequencing analysis was performed. Mutations in

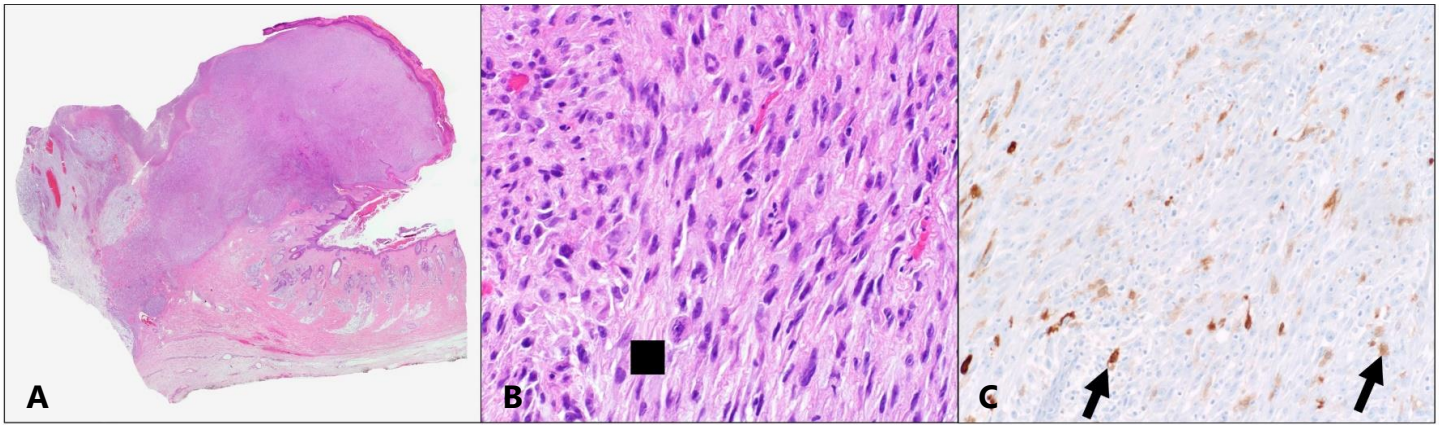

Figure 2. *Skin biopsy from an exophytic, bleeding mass on the scalp of a 53-year-old man.* ***A)*** *Skin biopsy of the enlarging, exophytic mass (H&E, 40× panoramic), showing* ***B)*** *an atypical intradermal proliferation of pleomorphic cells with multinucleate forms and widespread mitotic figures (square), (H&E, 200×).* ***C)*** *Patchy S100 immunostaining (arrows) of interstitial dendritic cells and Schwann cells, 200×.*

PIK3CA, *TET2*, *FAT1*, *CDKN2A*, *MDM2*, *CDK4*, *NOTCH1*, *SMARCA4*, *ASXL1*, and *TP53* were identified (**Table 1**), a mutational profile compatible with a molecular signature of AFX/PDS.

Subsequent wide local excision and staging workup was pursued to determine the extent of disease. Although imaging excluded calvarial invasion, positron emission tomography-computed tomography revealed increased uptake in axillary and cervical lymph nodes. Fine needle aspiration of cervical lymph nodes confirmed nodal metastasis. Given the metastatic progression, the patient was diagnosed with pleomorphic dermal sarcoma and treated with adjuvant pembrolizumab.

Case Discussion

The World Health Organization Classification of Tumors of Soft Tissue and Bone categorizes AFX as a dermal-based tumor of uncertain lineage, separate from the appellation PDS (also known as

Table 1. *Mutations detected in this patient's tumor.*

Gene	Transcript	Coding Variant	Protein Change	Variant Allele Fraction	Clinical significance
PIK3CA	NM_006218	c.1624G>A	p.E542K	36%	Yes
TET2	NM_001127208	c.3860T>C	p.F1287S	18%	Yes
FAT1	NM_005245	c.8928G>A	p.W2976*	18%	Yes
CDKN2A_p16	NM_000077	c.171>172delinsTT	p.R58*	26%	Yes
CDKN2A_p14	NM_058195	c.214_215delinsTT	p.P72L	26%	Yes
NOTCH1	NM_017617	c.4198C>T	p.Q1400*	23%	Yes
TP53	NM_000546	c.740_742delinsTTT	p.N247_R248delinsIW	11%	Yes
TP53	NM_000546	c.652G>A	p.V218M	11%	Yes
SMARCA4	NM_001128844	c.2644G>A	p.E882K	13%	Yes
ASXL1	NM_015338	c.1276dupA	p.Q428Tfs*10	5%	Yes
TPR	NM_003292	c.3428C>T	p.S1143F	11%	Uncertain
IKBKE	NM_014002	c.1516C>T	p.L506F	16%	Uncertain
FBXO11	NM_025133	c.416C>T	p.P139L	5%	Uncertain
CASP8	NM_001080125	c.543T>A	p.F181L	19%	Uncertain
CTNNB1	NM_001098209	c.1162C>T	p.L388F	31%	Uncertain
EPHA3	NM_005233	c.406C>T	p.R136*	14%	Uncertain
PDGFRB	NM_002609	c.2560G>A	p.D854N	19%	Uncertain
EBF1	NM_024007	c.1313C>T	p.S438L	13%	Uncertain
MET	NM_001127500	c.2224C>T	p.P742S	15%	Uncertain
PCM1	NM_006197	c.785C>A	p.A262D	46%	Uncertain
PREX2	NM_024870	c.213+1G>A	Splice site exon 2	14%	Uncertain
RUNX1T1	NM_001198627	c.1423G>A	p.A475T	16%	Uncertain
NOTCH1	NM_017617	c.1181G>T	p.G394V	19%	Uncertain
GATA3	NM_001002295	c.401C>T	p.P134L	13%	Uncertain
KAT6B	NM_012330	c.2671G>A	p.E891K	11%	Uncertain
C11orf30	NM_001300942	c.1606C>T	p.R536W	58%	Uncertain
KDM5A	NM_001042603	c.1409G>A	p.W470*	14%	Uncertain
KMT2D	NM_003482	c.6749C>T	p.P2250L	17%	Uncertain
GLI1	NM_005269	c.365G>A	p.G122D	15%	Uncertain
COL1A1	NM_000088	c.1495G>A	p.D499N	18%	Uncertain
DOT1L	NM_032482	c.3878G>A	p.R1293K	13%	Uncertain
MN1	NM_002430	c.1228C>T	p.P410S	8%	Uncertain

undifferentiated pleomorphic sarcoma), which is a substitute for "malignant fibrous histiocytoma." Risk factors include ultraviolet radiation, immunosuppression, ionized radiation, and skin trauma [10]. Historically, the usage of different monikers contributed to challenges in defining these entities. Limited histopathologic criteria are uniformly accepted to differentiate PDS from AFX: namely, greater depth of invasion (e.g. subcutaneous), lymphovascular or perineural invasion, and necrosis [9]. Although the exact incidences of AFX and PDS are unknown, it is estimated that 0.24% of skin cancers treated with Mohs Micrographic Surgery are diagnosed as AFX [11].

Atypical fibroxanthoma and PDS clinically simulate more commonly observed skin cancers, generally in older patients. Literature review revealed 33 cases of AFX and one case of PDS in which incongruent clinical diagnoses were rendered prior to histopathological analysis (**Table 2**), [10-35]. Of 26 men and 8 women between 11 and 90 years of age, lesions were most commonly reported as ulcerated tumors (58%), located on the face (42%), scalp (31%), and ear (23%), with a median duration of onset of three months. The most common pre-operative clinical diagnoses included squamous cell carcinoma (53%), basal cell carcinoma (45%), and melanocytic tumor/melanoma (45%).

Diagnosis of AFX and PDS is based on histopathologic analysis. Histopathology generally reveals hyperchromatic, pleomorphic spindle cells with multinucleate cells or foamy cytoplasmic alteration in close apposition to the epidermis. AFX can exhibit disparate microscopic patterns with cytological features that encompass spindled, clear, or osteoclastic cells, coupled with oddities in stromal alteration such as keloidal/desmoplastic collagen, hypervascularity, regression, and lymphoid aggregates. The histological diagnosis of AFX/PDS requires immunostaining to arrive at a precise diagnosis, mainly to exclude other malignant simulants,

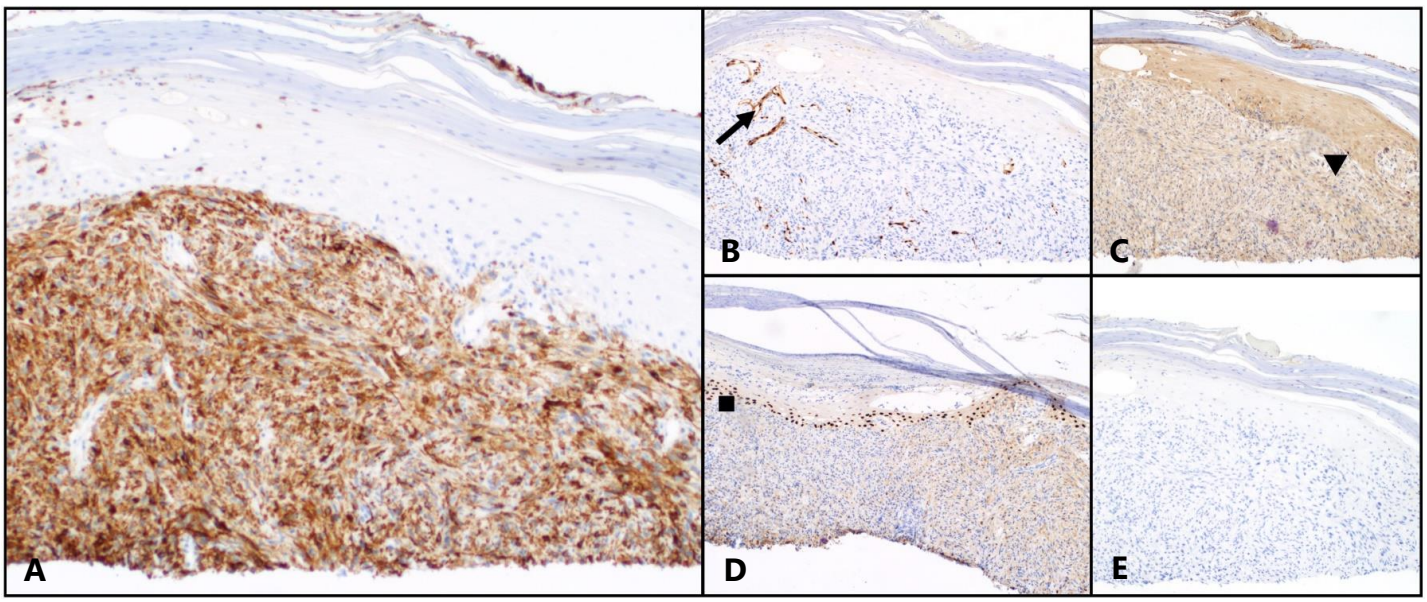

Figure 3. *Immunostaining of a biopsy of an exophytic mass on the scalp of a 53-year-old man.* ***A)*** *Immunostaining reveals diffuse expression of CD10 in tumor cells (100×).* ***B)*** *Atypical cells are importantly negative for erythroblast transformation-specific-related gene (ERG), (arrow denotes only positive staining of internal control: blood vessels; 100×).* ***C)*** *Staining is negative for SOX10 (triangle denotes only positive staining in internal control: melanocytes; 100×).* ***D)*** *Staining is negative for p63 (square denotes positive staining of internal control: basal keratinocytes; 100×).* ***E)*** *Staining is negative for desmin (100×).*

especially when spindled morphology predominates. Negative staining with high and low molecular weight cytokeratins (CK AE1/AE3, CK5/6, CK7), or more efficiently p63 or p40, can exclude sarcomatoid squamous cell carcinoma, whereas neurocristic markers S100 and SOX10 can be utilized to exclude desmoplastic melanoma (**Table 2**). The constituent tumor cells may be positive for procollagen-1, CD10, CD68, CD99, and SMA. Importantly, these markers may be positive in other sarcomatoid tumors and are only meaningful after negative expression for SOX10/S100 or cytokeratins/p63/p40 [36]. Desmin and ERG should be considerations to exclude leiomyosarcoma and spindled angiosarcoma, respectively. The point of pursuing a combination of neurocristic markers (S100/SOX10) is to exclude rare cases with focal expression of either marker that could be classified as de-differentiated melanoma or sarcomatoid melanoma, which represents a key pitfall in the differential diagnosis of AFX.

Sarcomatoid de-differentiation of melanoma may be indistinguishable from PDS, as was recently observed in a case of pure-type desmoplastic melanoma with dedifferentiation [37]. Rarely, AFX/PDS may be difficult to distinguish from melanoma and typically this conundrum arises if biphenotypic histomorphology (e.g. epithelioid and spindled) or biphenotypic immunostaining is observed, whereby a diagnosis of de-differentiated melanoma is posited. Sarcomatoid melanoma is a rare occurrence, but melanoma may display plasticity with loss of the typical immunohistochemical expression profile or show limited preservation of S100/SOX10. In instances of PDS with patchy S100 staining, as in our patient's case, the diagnosis must be differentiated from sarcomatoid dedifferentiated melanoma, especially given the difference in treatment and prognosis for the two diseases.

Complicating matters, a reported pitfall in AFX/PDS is aberrant expression of Melan-A [38]. Surrogate immunostains such as WT1, p75, or CD56 may be utilized in ambiguous scenarios, but genetic testing provides information that solves this dilemma [39]. Our case showed patchy S100 expression in PDS, attributed to interstitial dendritic or Schwann cells that has been similarly reported as a pitfall [12]. However, the diagnosis of record on resection was "nodular melanoma," sparking concern for de-differentiated melanoma [24].

To substantiate the diagnosis of AFX/PDS and exclude melanoma, next-generation sequencing analysis of 400 gene targets was performed at our institution. Four studies to date have investigated the genomic landscape of AFX and PDS [40–43]. Griewank et al. focused exclusively on TERT promoter mutations in AFX/PDS [41]. The other three articles utilized different sequencing approaches to capture the genetic signature of AFX/PDS. Our case mirrors the published genetic profiles of AFX/PDS, namely with mutations/deletions in *CDKN2A* (encoding P16 and P14arf), *NOTCH1*, *FAT1*, *CDK4*, *MDM2*, and *TP53* (**Table 1**), [40, 42, 43]. Lai et al. utilized whole exome and RNA-sequencing of eight matched AFX tumor-normal samples and found co-deletions of *CDKN2A* and *MTAP*, as well as mutations in *FAT1*, *COL11A1*, *CSMD3*, and *ERBB4*. Gene expression analysis also showed p53 pathway down-regulation, which is likely precipitated by *CDKN2A* inactivation [43]. Mutations in *FAT1*, a tumor suppressor, have also been found in upwards of 50% of AFX/PDS published cases, as well as our case (**Table 1**), [40]. The utility of next-generation sequencing in diagnosing AFX/PDS during clinically and histopathologically ambiguous scenarios cannot be overstated, especially when AFX/PDS may only be distinguished from de-differentiated

melanoma by genomic signature. Using these deep sequencing technologies, it is now accepted that AFX/PDS represents a spectrum, which provides clarity to a longstanding debate [40].

AFX/PDS may be more prevalent and have worse clinical outcomes in immunocompromised patients [8]. A single-center study reported that the incidence of AFX was as high as 78 per 100,000 renal transplant patients [44]. A review of the literature revealed 21 cases of AFX/PDS in patients with chronically immunosuppressed states (**Table 3**), [25, 30, 44-56]. These included nine cases of transplant immunosuppression, seven cases of chronic lymphocytic leukemia, three cases of HIV (including our case), and one case of mycosis fungoides. An important aspect for future study is how immunosuppression alters the tumor microenvironment when compared to immunocompetent hosts, which subsequently impacts tumor progression.

Conclusion

Our case emphasizes the potentially aggressive nature of AFX/PDS in immunosuppressed individuals and highlights the importance of understanding the genomic landscape for AFX/PDS to overcome immunostaining pitfalls. A combination of neurocristic markers should be utilized to exclude rare cases with focal expression of S100, HMB45, and/or SOX10 that could be classified as de-differentiated melanoma or sarcomatoid melanoma. Genomic sequencing can permit a definitive diagnosis when adequate tumor and technology is available. As sequencing technologies improve and become more accessible, they can be harnessed to better characterize malignant tumors when clinical and histopathological findings remain equivocal or pitfalls stoke diagnostic debate.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Helwig EB. Atypical fibroxanthoma. *Tex State J Med*. 1963;664. [PMID and DOI unavailable].
2. Fretzin DF, Helwig EB. Atypical fibroxanthoma of the skin. A clinicopathologic study of 140 cases. *Cancer*. 1973;31:1541–52. [PMID: 4709969].
3. Sankar NM, Pang KS, Thiruchelvam T, Meldrum-Hanna WG. Metastasis from atypical fibroxanthoma of skin. *Med J Aust*. 1998;168:418–19. [PMID: 9594957].
4. Miller K, Goodlad JR, Brenn T. Pleomorphic dermal sarcoma: adverse histologic features predict aggressive behavior and allow distinction from atypical fibroxanthoma. *Am J Surg Pathol*. 2012;36:1317–26. [PMID: 22510760].
5. Polcz MM, Sebaratnam DF, Fernández-Peñas P. Atypical fibroxanthoma management: Recurrence, metastasis and disease-specific death. *Australas J Dermatol*. 2018;59:10–25. [PMID: 28815551].
6. Koch M, Freundl AJ, Agaimy A, et al. Atypical fibroxanthoma-Histological diagnosis, immunohistochemical markers and concepts of therapy. *Anticancer Res*. 2015;35:5717–35. [PMID: 26503993].
7. Ang GC, Roenigk RK, Otley CC, Kim Phillips P, Weaver AL. More than 2 decades of treating atypical fibroxanthoma at Mayo Clinic: What have we learned from 91 patients? *Dermatologic Surg*. 2009;35:765–72. [PMID: 19389106].
8. McCoppin HH, Christiansen D, Stasko T, et al. Clinical spectrum of atypical fibroxanthoma and undifferentiated pleomorphic sarcoma in solid organ transplant recipients: A collective experience. *Dermatologic Surg*. 2012;38:230–29. [PMID: 22129349].
9. Jo VY, Fletcher CDM. WHO classification of soft tissue tumours: An update based on the 2013 (4th) edition. *Pathology*. 2014;46:95–104. [PMID: 24378391].
10. Mahalingam S, Shah A, Stewart A. Atypical Fibroxanthoma: A case series and review of literature. *Auris Nasus Larynx*. 2015;42:469–71. [PMID: 25912604].
11. Anderson HL, Joseph AK. A pilot feasibility study of a rare skin tumor database. *Dermatologic Surg*. 2007;33:693–96. [PMID: 17550446].
12. Melendez MM, Xu X, McClain SA, Huang SI. Atypical fibroxanthoma in a young woman: An unusual case presentation. *Can J Plast Surg*. 2007;15:169–72. [PMID: 19554152].
13. Inskip M, Magee J, Weedon D, Rosendahl C. Atypical fibroxanthoma of the cheek-case report with dermatoscopy

and dermatopathology. *Dermatol Pract Concept*. 2014;4:77–80. [PMID: 24855581].

14. Pagliarello C, Peccerillo F, Zucchi A, et al. Lesion presenting with a "blue amber" pattern. *World J Clin Cases*. 2016;4:333–35. [PMID: 27803916].
15. Pesapane F, Nazzaro G, Lunardon L, Coggi A, Gianotti R. Two friends with eroded nodules on the ears: Atypical fibroxanthoma case report. *An Bras Dermatol*. 2015;90:577–79. [PMID: 26375231].
16. Rathore D, Mohyudin MN, Mehta P, Ahluwalia HS. Atypical fibroxanthoma of the medial canthus: A rare presentation. *Orbit*. 2013;32:194–96. [PMID: 23514046].
17. Lazaro-Santander R, Andres-Gozalbo C, Rodriguez-Pereira C, Vera-Roman JM. Clear cell atypical fibroxanthoma. *Histopathology*. 1999;35:484–85. [PMID: 10583571].
18. Nguyen CM, Chong K, Cassarino D. Clear cell atypical fibroxanthoma: A case report and review of the literature. *J Cutan Pathol*. 2016;43:538–42. [PMID: 26956561].
19. Dudelzak J, Sheehan DJ, Mullins SC, Peterson CM. Malignant perifollicular atypical fibroxanthoma treated with Mohs surgery. *Dermatologic Surg*. 2007;33:364–68. [PMID: 17338699].
20. Lee S, Joo KB, Park CK, Kim TS, Bae J. A case of atypical fibroxanthoma of subungual type: Ultrasound and magnetic resonance imaging findings. *Clin Imaging*. 2013;37:155–58. [PMID: 23206624].
21. Sharma SR, Meligonis G, Todd P. Uncommon skin cancer: pleomorphic dermal sarcoma. *BMJ Case Rep*. 2018;2018. [PMID: 29507037].
22. Diaz-Cascajo C, Borghi S, Bonczkowitz M. Pigmented atypical fibroxanthoma. *Histopathology*. 1998;33:537–41. [PMID: 9870148].
23. Rovere RK, Hilgert SF, da Costa PC, de Lima AS. A rare neoplastic growth on the ear lobe. *Klin Onkol*. 2014;27:367–68. [PMID: 25312715].
24. Agaimy A, Specht K, Stoehr R, et al. Metastatic malignant melanoma with complete loss of differentiation markers (undifferentiated/dedifferentiated melanoma) analysis of 14 patients emphasizing phenotypic plasticity and the value of molecular testing as surrogate diagnostic marker. *Am J Surg Pathol*. 2016;40:181–91. [PMID: 26448190].
25. Kanitakis J, Euvrard S, Montazeri A, Garnier JL, Claudy A. Atypical fibroxanthoma in a renal transplant recipient. *J Am Acad Dermatol*. 1996;35(2 Pt 1):262–64. [PMID: 8708032].
26. Goette DK, Odom RB. Atypical fibroxanthoma masquerading as pyogenic granuloma. *Arch Dermatol*. 1976;112:1155–57. [PMID: 952539].
27. González-Vela MC, Salcedo W, Neira C, et al. Atypical fibroxanthoma developing on a pacemaker pocket mimicking a pyogenic granuloma. *Cardiovasc Pathol*. 2013;22:102–04. [PMID: 22502867].
28. Sachdev R, Goel RK, Gajendra S. Atypical fibroxanthoma of scalp: A paradoxical benign tumour. *J Clin Diagn Res*. 2015;9:EL02-03. [PMID: 26816908].
29. Pujani M, Hassan MJ, Jetley S. Atypical fibroxanthoma in a young female misdiagnosed clinically as a malignant melanoma--an unusual presentation. *J Cancer Res Ther*. 2015;11:1027. [PMID: 26881598].
30. Perrett CM, Cerio R, Proby CM, Harwood CA. Atypical fibroxanthoma in a renal transplant recipient. *Histopathology*. 2005;47:326–27. [PMID: 16115238].
31. Goldstein Z, Sarantopoulos G, Smart C. Clear-cell atypical fibroxanthoma: An unusual case in an unusual place. *J Cutan Pathol*. 2017;44:951–53. [PMID: 28753253].
32. Yi-Hsin H, Cheng-Sheng C. Keloidal atypical fibroxanthoma on the back of an 80-year-old man, pitfalls in the clinical and histological diagnosis. *Indian J Dermatol Venereol Leprol*. 2012;78:409. [PMID: 22565465].
33. Nakai N, Takenaka H, Kishimoto S. Atypical fibroxanthoma on a bald scalp. *J Dermatol*. 2005;32:848–51. [PMID: 16361741].
34. Requena L, Sangueza OP, Yus ES, Furio V. Clear-cell atypical fibroxanthoma: an uncommon histopathologic variant of atypical fibroxanthoma. *J Cutan Pathol*. 1997;24:176–82. [PMID: 9085154].
35. Rice CD, Gross DJ, Dinehart SM, Brown HH. Atypical Fibroxanthoma of the Eyelid and Cheek. *Arch Ophthalmol*. 1991;109:922–23. [PMID: 2064569].
36. Scolyer RA, Murali R, McCarthy SW, Thompson JF. Atypical fibroxanthoma: differential diagnosis from other sarcomatoid skin lesions. *Diagnostic Histopathol*. 2010;16:401–08. [DOI: 10.1016/j.mpdhp.2010.06.007].
37. Kiuru M, McDermott G, Berger M, Halpern A, Busam K. Desmoplastic melanoma with sarcomatoid dedifferentiation. *Am J Surg Pathol*. 2014;38:864–70. [PMID: 24618614].
38. Thum C, Hollowood K, Birch J, Goodlad J, Brenn T. Aberrant Melan-A expression in atypical fibroxanthoma and undifferentiated pleomorphic sarcoma of the skin. *J Cutan Pathol*. 2011;38:954–60. [PMID: 22050092].
39. Fraga G. Diagnosis of Sarcomatoid Melanoma by Surrogate Immunostains. *Am J Dermatopathol*. 2018;40:304–05. [PMID: 28937436].
40. Griewank KG, Wiesner T, Murali R, et al. Atypical fibroxanthoma and pleomorphic dermal sarcoma harbor frequent NOTCH1/2 and FAT1 mutations and similar DNA copy number alteration profiles. *Mod Pathol*. 2018;31:418–28. [PMID: 29099504].
41. Griewank K, Schilling B, Murali R, et al. TERT promoter mutations are frequent in atypical fibroxanthomas and pleomorphic dermal sarcomas. *Mod Pathol*. 2014;27:502–08. [PMID: 24030750].
42. Helbig D, Ihle MA, Pütz K, et al. Oncogene and therapeutic target analyses in atypical fibroxanthomas and pleomorphic dermal sarcomas. *Oncotarget*. 2016;7:21763–74. [PMID: 26943575].
43. Lai K, Harwood CA, Purdie KJ, et al. Genomic analysis of atypical fibroxanthoma. *PLoS One*. 2017;12: e0188272. [PMID: 29141020].
44. Hafner J, Kunzi W, Weinreich T. Malignant fibrous histiocytoma and atypical fibroxanthoma in renal transplant recipients. *Dermatology*. 1999;198:29–32. [PMID: 10026398].
45. Paquet P, Piérard GE. Invasive atypical fibroxanthoma and eruptive actinic keratoses in a heart transplant patient.

Dermatology. 1996;192:411–13. [PMID: 8864396].

46. Ferri E, Iaderosa GA, Armato E. Atypical fibroxanthoma of the external ear in a cardiac transplant recipient: case report and the causal role of the immunosuppressive therapy. *Auris Nasus Larynx*. 2008;35:260–63. [PMID: 17804184].
47. Cooper JZ, Newman SR, Scott GA, Brown MD. Metastasizing atypical fibroxanthoma (cutaneous malignant histiocytoma): report of five cases. *Dermatol Surg*. 2005;31:221–25. [PMID: 15762219].
48. Konda S, Patel VA, O'Bryan KW, Ratner D. Fibrohistiocytic tumors in a lung transplant patient taking oral capecitabine for nonmelanoma skin cancer chemoprevention. *Dermatol Surg*. 2014;40:807–10. [PMID: 24927001].
49. Perrett CM, Macedo C, Francis N, Ion L, Bunker CB. Atypical fibroxanthoma in an HIV-infected individual. *J Cutan Pathol*. 2011;38:357–59. [PMID: 20973809].
50. Kovach BT, Sams HH, Stasko T. Multiple atypical fibroxanthomas in a cardiac transplant recipient. *Dermatol Surg*. 2005;31:467–70. [PMID: 15871326].
51. Colgan MB, Brewer JD, Weaver AL, Roenigk RK, Otley CC. Atypical fibroxanthoma in the setting of chronic lymphocytic leukemia and other non-hodgkin lymphomas. *Dermatol Surg*. 2011;37:671–76. [PMID: 21446993].
52. Avshalumov K, Williford P, Sangueza OP, Goldenberg G. Atypical fibroxanthoma presenting in a patient with stage III mycosis fungoides. *J Dermatolog Treat*. 2008;19:118–20. [PMID: 18484429].
53. Kemp JD, Stenn KS, Arons M, Fischer J. Metastasizing atypical fibroxanthoma. Coexistence with chronic lymphocytic leukemia. *Arch Dermatol*. 1978;114:1533–35. [PMID: 718196].
54. Blatière V, De Boever CM, Jacot W, Durand L, Guillot B. Cutaneous malignant fibrous histiocytoma in an HIV-positive patient. *J Eur Acad Dermatol Venereol*. 2007;21:106–07. [PMID: 17207179].
55. Stein A, Hackert I, Sebastian G, Meurer M. Cutaneous malignant fibrous histiocytoma of the scalp in a renal transplant recipient. *Br J Dermatol*. 2006;154:183–85. [PMID: 16403118].
56. Nergard J, Glener J, Reimer D, Greenwald JS. Atypical fibroxanthoma of the scalp with recurrent and multiple regional cutaneous metastases. *JAAD Case Reports*. 2016;2:491–93. [PMID: 27981227].

Table 2. *Characteristics of atypical fibroxanthomas and pleomorphic dermal sarcomas with incongruent clinical diagnoses prior to histopathologic analysis published in the literature.*

N, R†	A	S	L	Clinical presentation	D	PMH	Clinical diagnosis	Histological diagnosis	Immunohistochemical staining
1 [12]	21	F	Face	14-millimeter pruritic, enlarging nodule with overlying telangiectasias	3	None	Acne	AFX	Pos: None Neg: HMB45, Melan-A, FXIIIa, AEP, CD31, S100 (limited focally positive areas), A1AC, A1AT, NK1, CD68
2 [13]	73	M	Face	15x10-millimeter, deep red, slightly domed lesion	1.5	Basal cell carcinoma, squamous cell carcinoma	Amelanotic melanoma, Merkel cell carcinoma, squamous cell carcinoma,	AFX	Pos: CD68 Neg: S100, CK AE1/AE3, HMWCK
3 [14]	69	F	Face	Violaceous nodule	2	Hypertension	Basal cell carcinoma	AFX	ND
4 [15]	75	M	Ear	1.5-centimeter oval-shaped, exophytic, bleeding nodule	2	ND	Basal cell carcinoma	AFX	Pos: CD68, CD163, FXIII, SMA, Neg: S100, Melan-A, HMB45
5 [15]	78	M	Ear	1-centimeter juicy red, dome-shaped nodule	12	Basal cell carcinoma	Basal cell carcinoma	AFX	Pos: CD68, CD163, FXIII, SMA, Neg: S100, Melan-A, HMB45
6 [16]	90	F	Face	15x15-millimeter exuberant mass	ND	ND	Basal cell carcinoma	AFX	Pos: CD10 Neg: p63, CK AE1/AE3, S100
7 [17]	90	F	Face	25x15-millimeter ulcerated nodule	4	ND	Basal cell carcinoma	AFX (clear cell variant)	Pos: Vim, CD68 Neg: S100, HMB45, FXIIIa, Des, SMA, CK AE1/AE3, EMA, CEA, CD45, CD3, CD20, CD34
8 [18]	49	M	Ear	1.6-centimeter friable, ulcerated nodule with underlying beefy red skin and hemorrhagic crust	0.75	None	Cellulitis	AFX (clear cell variant)	Pos: CD10, CD68 Neg: CK AE1/AE3, CK5/6, CK7, p63, EMA, S100, Melan-A

9 [19]	43	M	Face	1-centimeter erythematous, firm, domed nodule	8	ND	Follicular inclusion cyst, squamous cell carcinoma	AFX	Pos: CD10, CD68 Neg: S100, CK AE1/AE3, CD34
10 [20]	56	M	Toe	1-centimeter tender, swollen, and peduncular mass	5	ND	Keratoacanthoma, malignant melanoma, squamous cell carcinoma	AFX	Pos: Vim, CD10, CD99, HLA-DR, CD68, p53 Neg: CK AE1/AE3, EMA, HMB45, S100, SMA, Des, Myoglobin, MyoD1, p63, CD34
11 [21]	86	M	Scalp	9 × 13-millimeter raised lesion with overlying crust and rolled edges	2.5	Squamous cell carcinoma	Keratoacanthoma, squamous cell carcinoma	PDS	Pos: SMA Neg: CK AE1/AE3, S100, Des, CD31, CD34, p63
12 [22]	ND	M	ND	ND	ND	ND	Malignant melanoma	AFX (pigmented variant)	Pos: Vim, CD68 (weak) Neg: CD34, Des, HMB45, NK1/C3, CK AE1/AE3, BerH2, Lyz, A1AC
13 [22]	ND	M	ND	ND	ND	ND	Malignant melanoma	AFX (pigmented variant)	Pos: Vim, CD68 (weak) Neg: S100, CD34, Des, HMB45, NK1/C3, CK AE1/AE3, BerH2, Lyz, A1AC.
14 [23]	83	F	Ear	Erythematous violaceous infiltrative, ulcerated onion-like mass with hyperkeratotic surface and prominent vessels	ND	ND	Malignant melanoma (metastatic)	AFX	Pos: None Neg: S100, CK AE1/AE3, Melan-A, p53, CD23, Des
15 [22]	ND	M	ND	ND	ND	ND	Melanocytic tumor	AFX (pigmented variant)	Pos: Vim, CD68 (weak) Neg: S100, CD34, Des, HMB45, NK1/C3, CK AE1/AE3, BerH2, Lyz, A1AC.
16 [24]	11	M	Neck	4-millimeter, crusted, pink papule	3	ND	Molluscum contagiosum, pyogenic granuloma, nevus	AFX	Pos: CD10, CD68, Vim Neg: S100, CK AE1/AE3, SMA, CD31
17 [25]	46	F	Face	1.5-centimeter white nodule	ND	Renal transplant	Nevus	AFX	Pos: Vim, CK AE1/AE3 (weak) Neg: CD34, S100

18 [26]	82	M	Ear	1.5-centimeter split, hemispheric, bright red, moderately firm, bleeding papule	1.25	Actinic keratoses, sebaceous hyperplasias	Pyogenic granuloma	AFX	ND
19 [27]	89	M	Chest	2.5-centimeter exophytic, yellow, ulcerated nodule	ND	ND	Pyogenic granuloma	AFX	Pos: CD10, CD99, CD68, and SMA Neg: CK AE1/AE3, CAM5.2, S100, Melan-A, Des, CDP63, CD31, and HHV-8 LNA-1.
20 [28]	81	M	Scalp	5x3-centimeter enlarging nodulo-ulcerative lesion with bleeding edges	90	ND	Sebaceous carcinoma	AFX	Pos: Vim, CD68, CD10 Neg: CK AE1/AE3, EMA, SMA, Des, Caldesmon, HMB45
21 [29]	24	F	Leg	2x1.5-centimeter firm, brown nodule	2	ND	Squamous cell carcinoma	AFX	Pos: A1AT, CD68 Neg: CK AE1/AE3, HMB45
22 [30]	44	M	Neck	15-millimeter, tender, red, ulcerated nodule	ND	Renal transplant	Squamous cell carcinoma	AFX	Pos: Vim, CD99 Neg: CK AE1/AE3, S100, CD15, CD34, CD68, MNF 116, SMA, HMB45, Des, PGP 9.5, A1AC, KP1, FXIIIa.
23 [10]	58	M	Scalp	20x22-millimeter central dome shaped lesion	ND	Solar keratosis	Squamous cell carcinoma	AFX	Pos: Actin Neg: CAM5.2, CK5/6, CD34, Melan-A, S100
24 [10]	63	F	Face	6x6-millimeter ulcerated lesion	ND	Solar keratosis, basal cell carcinoma	Squamous cell carcinoma	AFX	Pos: CD10 Neg: CAM 5.2, CD34, Melan-A, S100, HMB45, CK AE1/AE3
25 [31]	72	M	Leg	Ulcerated nodule	ND	Non-melanoma skin cancers, warthin tumor of parotid gland	Squamous cell carcinoma	AFX (clear cell variant)	Pos: CD10, CD68 Neg: Tyr, CD34, AR, KRT5, KRT6, EMA, CAM5.2, MART-1, SOX10, S100, CK AE1/AE3, P40, HMB-45 and MSA.
26 [10]	77	M	Scalp	10x8-millimeter amelanotic nodule	ND	None	Squamous cell carcinoma	AFX	Pos: CD10 Neg: CAM 5.2, CK 5/6, CD34, Melan-A, HMB45, CK903

27 [10]	79	M	Face	10x6-millimeter crusting nodule	ND	Solar keratosis	Squamous cell carcinoma	AFX	Pos: Actin, CD10 Neg: CAM 5.2, Melan-A, CK903, EMA, Des
28 [32]	80	M	Back	7×5-centimeter ill-defined, firm and violaceous plaque	3	Parkinsonism, hypertension, hyperlipidemia	Squamous cell carcinoma	AFX (keloidal variant)	Pos: Vim, CD10, SMA, CD68, CD99 Neg: CK AE1/AE3, S100, HMB45, CD31, FXIIIa, Des
29 [33]	81	M	Scalp	11-millimeter solitary, domed, red, ulcerated nodule	4	Basal cell carcinoma	Squamous cell carcinoma	AFX	Pos: Vim, HHF-35, CD68 Neg: S100, HMB45, FVIII, CD31, CD34, CK AE1/AE3
30 [34]	81	M	Face	3x4-centimeter ulcerated nodule	3	ND	Squamous cell carcinoma	AFX (clear cell variant)	Pos: Vim, MSA, SMA Neg: S100, Des, EMA, CK AE1/AE3, CEA
31 [35]	82	M	Face (eye)	3-centimeter lesion with ectropion, exposure conjunctivitis, and eyelash loss	1.5	ND	Squamous cell carcinoma	AFX	Pos: Vim Neg: S100, CK AE1/AE3
32 [10]	82	M	Scalp	5x6-millimeter crusting, ulcerated lesion	ND	Solar keratosis	Squamous cell carcinoma	AFX	Pos: Vim, CD68 Neg: CAM 5.2, Melan-A, S100, HMB45, CK AE1/AE3, EMA
33 [10]	83	M	Scalp	3x3-millimeter bleeding, ulcerated lesion	ND	Basal cell carcinoma	Squamous cell carcinoma	AFX	Pos: Vim Neg: CAM 5.2, Melan-A, S100, HMB45, CK AE1/AE3
34 [10]	89	M	Scalp	8x8-millimeter bleeding, ulcerated lesion	ND	None	Squamous cell carcinoma	AFX	Pos: CD68 Neg: CAM5.2, CK5/6, CD34, Melan-A, HMB45, EMA

†A: Age (years); AFX: Atypical fibroxanthoma; D: Duration (months); Dx: Diagnosis; F: Female; L: Location; M: Male; N: Number; ND: Not described; Neg: Negative staining for; PDS: Pleomorphic dermal sarcoma; PMH: Past medical history; Pos: Positive staining for; R: Reference; S: Sex.

Table 3. *Characteristics of atypical fibroxanthomas and pleomorphic dermal sarcomas in immunosuppressed patients.*

N, R†	A	G	L	Clinical Presentation	D	PMH	Dx	Associated Skin Findings	Prognosis
1 [30]	44	M	Neck	15-millimeter, tender, red, ulcerated nodule	ND	Renal transplant (on azathioprine, cyclosporine, and prednisone)	AFX	Developed SCCs, BCCs, SCC in situ, and viral warts	No recurrence
2 [25]	46	F	Face	1.5-centimeter white nodule that recurred following initial excision	ND	Renal transplant (on azathioprine, cyclosporine, and steroids)	AFX	Developed Bowen disease and SCC	ND
3 [44]	57	M	Face	ND	ND	Renal transplant (on azathioprine and prednisone)	AFX	None	Recurrence
4 [45]	65	M	Face	Erythematous, fleshy tumor	ND	Cardiac transplant (on azathioprine, cyclosporine, and methylprednisolone)	AFX	Developed multiple eruptive actinic keratoses	Local recurrence with deep dermal invasion
5 [46]	66	M	Ear	1.5-centimeter painless cutaneous nodule	6	Cardiac transplant (on cyclosporine and prednisone)	AFX	Developed multiple actinic keratosis and SCCs	No recurrence (18-month follow-up)
6 [47]	66	M	Upper extremity	ND	ND	Chronic lymphocytic leukemia (undergoing chemotherapy during AFX diagnosis)	AFX	None	No recurrence (48-month follow-up)
7 [48]	67	ND	Face (1) and scalp (2)	ND	ND	Lung transplant (on acitretin, capecitabine, tacrolimus, mycophenolate mofetil, prednisone)	AFX, PDS	Developed multiple SCCs and BCCs	Died of graft-versus-host-disease
8 [49]	71	M	Scalp	Exophytic ulcerated nodule	ND	Human Immunodeficiency Virus (CD4 280, undetectable viral load)	AFX	None	ND
9 [50]	75	M	Face (2) and scalp (1)	7-millimeter crusted papule; pink ulcerated papule	48	Cardiac transplant (on azathioprine, cyclosporine, and prednisone)	AFX	Developed multiple SCCs	No recurrence
10 [51]	76	M	Face	ND	ND	Chronic lymphocytic leukemia (diagnosed 6.8 years earlier)	AFX	None	No recurrence (94-month follow-up)
11 [51]	77	M	Scalp	ND	ND	Chronic lymphocytic leukemia (diagnosed 8.8 years earlier)	AFX	None	No recurrence

12 [52]	77	F	Hand	ND	ND	Mycosis fungoides (stage III), erythroderma	AFX	None	Local recurrence one year later
13 [53]	79	M	Face	2-centimeter hard, dark red nodule	ND	Chronic lymphocytic leukemia (concurrently diagnosed)	AFX	None	Recurrence and metastasis
14 [51]	80	M	Scalp	ND	ND	Chronic lymphocytic leukemia (diagnosed 2.4 years earlier)	AFX	None	No recurrence (162-month follow-up)
15 [51]	84	F	Back	ND	ND	Chronic lymphocytic leukemia (diagnosed 6.7 years earlier)	AFX	None	No recurrence (32-month follow-up)
16 [54]	49	M	Back	9-centimeter skin-colored, painless, mobile, firm nodule	3	Acquired Immune Deficiency Syndrome (CD4 120, HIV RNA was 130 copies/mL)	PDS	None	Metastasized to lungs
17 (CR)	53	M	Scalp	4-centimeter exophytic, bleeding mass	18	Acquired Immune Deficiency Syndrome	PDS	None	No recurrence
18 [55]	57	M	Scalp	15-millimeter skin tumor that recurred following resection as multiple nodules	ND	Renal transplant (on azathioprine, cyclosporine, and prednisolone)	PDS	None	Patient died from recurrence and metastasis to multiple internal organs
19 [44]	62	M	Upper extremity	ND	ND	Renal transplant (on azathioprine, cyclosporine, and prednisolone)	PDS	Developed multiple actinic keratosis and SCCs	3 local recurrences with extension to fascia
20 [44]	70	M	Lower extremity	2 x 2.5-centimeter nodule	ND	Renal transplant (on azathioprine, cyclosporine, and prednisone)	PDS	None	No recurrence (10-month follow-up)
21 [56]	82	M	Scalp	1.7-centimeter erythematous, tender, hyperkeratotic nodule	ND	Chronic lymphocytic leukemia	PDS	None	Local recurrence and metastases

†A: Age (years); AFX: Atypical fibroxanthoma; BCC: Basal cell carcinoma; CR: Current report; D: Duration (months); F: Female; Dx: Diagnosis; L: Location; M: Male; N: Number; ND: Not described; PMH: Past medical history; PDS: Pleomorphic dermal sarcoma; R: Reference; S: Sex; SCC: Squamous cell carcinoma.