CASE REPORT

Nagoya J. Med. Sci. **88**. 162–169, 2026
doi:10.18999/nagjms.88.1.162

A challenging case of giant atypical fibroxanthoma on non-chronically sun-damaged skin: a case report with TP53 somatic mutation (c.375+1 G>A)

Özge Zorlu[1], Sevil Karabağ[2] and Semih Aşıkovalı[3]

[1]*Department of Dermatology and Venerology, Medical Faculty, Tekirdağ Namık Kemal University, Tekirdağ, Turkey*
[2]*Department of Pathology, Medical Faculty, Tekirdağ Namık Kemal University, Tekirdağ, Turkey*
[3]*Department of Medical Genetics, Medical Faculty, Tekirdağ Namık Kemal University, Tekirdağ, Turkey*

ABSTRACT

Atypical fibroxanthoma (AFX) is a rare tumor of uncertain histogenetic origin, generally seen in elderly patients' chronically sun-damaged skin, most frequently in the head and neck region. Due to the absence of specific histopathologic features, AFX is a diagnosis of exclusion. Herein, we report clinical, histopathological, and molecular features of a young patient with a recurrent and giant AFX lesion on non-chronically sun-damaged skin. Histologically, the tumor was well-circumscribed, encapsulated, and dermal-based, composed of highly atypical and pleomorphic bizarre spindled cells with hyperchromatic and irregular nuclei and scarce multinucleated giant cells. There was no subcutaneous invasion, necrosis, or perineural/perivascular invasion. Tumoral cells were diffusely and strongly positive for CD10 but negative for melanocytic, cytokeratin, and muscle immunohistochemical markers. Almost five years after the excision, no recurrence and/or distant metastasis was observed. A pathogenic variant of a TP53 somatic mutation (c.375+1 G>A) was identified in the tumor.

Keywords: atypical fibroxanthoma, pleomorphic dermal sarcoma, recurrence, histopathology, TP53 somatic mutation

Abbreviations:
AFX: atypical fibroxanthoma
PDS: pleomorphic dermal sarcomas
IHC: immunohistochemistry
SCC: squamous cell carcinoma

INTRODUCTION

Atypical fibroxanthoma (AFX) is a rare intermediate-risk tumor of uncertain histogenetic origin, generally seen in elderly patients, with a predilection for males.[1-3] Clinically, the lesions often

Received: June 17, 2025; Accepted: August 26, 2025
Corresponding Author: Sevil Karabağ, MD
Department of Pathology, Medical Faculty, Tekirdağ Namık Kemal University,
Namık Kemal Neighborhood, Campus Street No:1, Tekirdağ 59100, Turkey
Tel: +90 532 1792484, E-mail: eesevil-krbg@hotmail.com, skarabag@nku.edu.tr

present as exophytic, dome-shaped, skin- to flesh-colored, rapidly growing nodules/plaques with central ulceration on chronically sun-damaged skin, most commonly on the head and neck region of elderly patients. The trunk and extremities are rarely affected but are involved in younger patients.[4] Tumor size can range between 0.6 and 3 cm.[1,3,4] Although UV damage is responsible for most AFX cases, there are other rare associated risk factors, including burning, trauma, scarring, immunosuppression, exposure to radiation, Li-Fraumeni syndrome, and xeroderma pigmentosum.[1,4-6]

For a definite diagnosis, the other diseases included in the differential diagnosis, such as pleomorphic dermal sarcomas (PDS), squamous cell carcinoma (SCC), amelanotic melanoma, leiomyosarcoma, and metastasis from internal malignancies, should be excluded. Histopathological and immunohistochemical (IHC) analyses are crucial for differential diagnosis. However, histopathological examination and diagnosis can be challenging due to shared immunophenotypes, especially with PDS.

Herein, we report the clinical, morphological, IHC, and molecular features of a 29-year-old male patient who had a recurrent AFX on his trunk with a TP53 somatic mutation.

CASE PRESENTATION

A 29-year-old male patient visited a general surgery outpatient clinic of another hospital with a complaint of a growing mass on his back (Fig. 1A). According to the patient's history, the lesion appeared as a small pimple, and its size gradually increased over two months. The lesion was excised completely. On IHC analysis, pan-cytokeratin, smooth muscle actin (SMA), desmin, CD31, CD34, CD68, LCA, S100, and HHV-8 were negative. No information regarding atypical mitosis, invasion depth, or perineural/perivascular invasion was specified in the histopathology report. According to the histopathological findings, the lesion was interpreted as a malignant

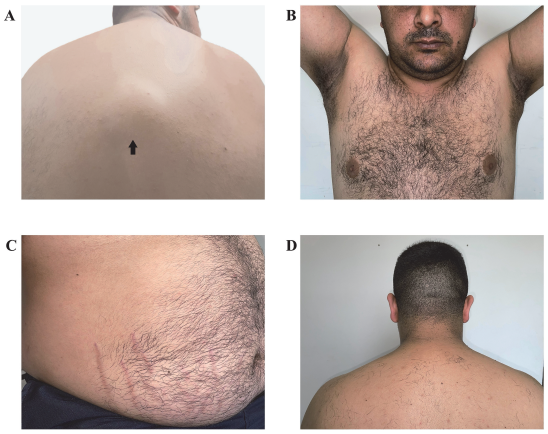

Fig. 1 Clinical pictures of the patient

Fig. 1A: A skin-colored mass without ulceration or epidermal change at the midline of the back. Photograph printed with patient permission.

Fig. 1B: Acanthosis nigricans on the armpits, periorbital hyperpigmentation, and freckles on the face. Photograph printed with patient permission.

Fig. 1C: Abdominal obesity and striae rubrae on the abdominal region. Photograph printed with patient permission.

Fig. 1D: Acanthosis nigricans and multiple acrochordons around the neck. Photograph printed with patient permission.

mesenchymal tumor with positive surgical margins. The findings were reviewed to corroborate the diagnosis of undifferentiated pleomorphic sarcoma. Re-excision was not performed.

The patient visited our dermatology outpatient clinic for a recurrence of the lesion that occurred almost one year later at the same location. However, the lesion grew faster this time. There was no chronic or intense intermittent sun exposure, sunburn in childhood, trauma, or burn history. He has been an indoor worker at a turnspit for 10 years. The patient was otherwise healthy. He was not taking any medication. There was no family history of similar lesions. His uncle died from larynx cancer. Dermatologic examination revealed an asymptomatic, skin-colored tumor without ulceration or epidermal change at the midline of the back, acanthosis nigricans on the armpits, neck, hand, and feet, striae rubrae on the abdominal region, multiple acrochordons around the neck, hyperpigmentation and freckles on the face, and abdominal obesity (Fig. 1B–D). The skin appendages were normal. Body mass index was 40.4.

The lesion was completely excised, and a histopathological examination was performed. Macroscopic examination revealed a sample measuring 14 × 9 × 7 cm, showing a yellow-brown colored homogeneous appearance and cystic and hemorrhagic areas in some places (Fig. 2A). Almost the entire tumor was sampled for microscopic examination, and each area appeared similar to the others. Histologically, a well-circumscribed, encapsulated, dermal-based tumor composed of highly atypical and pleomorphic bizarre spindled cells with hyperchromatic and irregular nuclei and scarce multinucleated giant cells on a keloid-like sclerotic background was observed. There was no subcutaneous invasion, necrosis, or perineural/perivascular invasion. Histopathological features of the case are shown in Figs. 2B–D and 3A. Surgical margins were

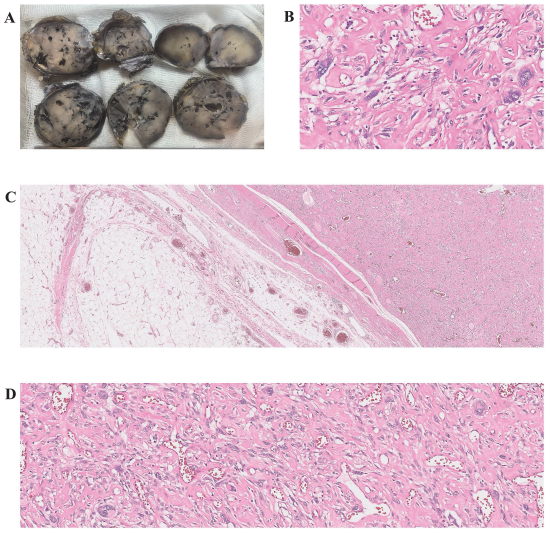

Fig. 2 Macroscopic and histopathological features (hematoxylin and eosin [H & E])

Fig. 2A: Macroscopic slices of the tumor. Yellow-brown colored homogeneous appearance and cystic and hemorrhagic areas in some areas.

Fig. 2B: Atypical and pleomorphic bizarre spindled cells with hyperchromatic and irregular nuclei and scarce multinucleated giant cells on a sclerotic background (H & E, 400x)

Fig. 2C: Well-circumscribed, encapsulated tumor without subcutaneous invasion, necrosis, or perineural/perivascular invasion (H & E, 10x)

Fig. 2D: Atypical and pleomorphic bizarre spindled cells and multinucleated giant cells on a sclerotic background (H&E, 100x)

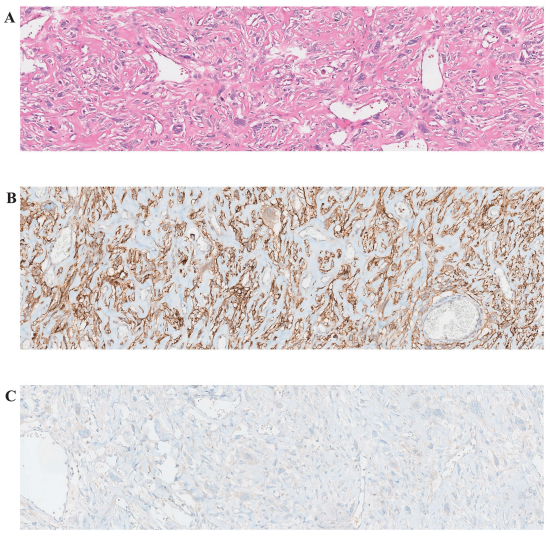

Fig. 3 Histopathological features
Fig. 3A: Hematoxylin and eosin (H & E) staining of the lesion (100x)
Fig. 3B: Diffuse and strong CD10 positivity in tumor cells (100x)
Fig. 3C: Tumor cells were negative for P53 (100x).

clear. Histopathological and IHC features of the case in Fig. 3B and 3C. IHC studies showed that lesional cells were diffusely and strongly positive for CD10 (Fig. 3B) and negative for EMA, SATB2, SMA, S100, desmin, CD68, INI-1, pancytokeratin, myogenin, P53 (Fig. 3C), HMB45, Melan-A, CD34, CD31, ERG, FLI-1, and CD21. Based on the demarcation from the surrounding tissue, the absence of atypical mitoses and perineural/perivascular invasion, and the IHC features, the case was diagnosed as AFX. The patient underwent a positron emission tomography computed tomography (PET CT) for metastasis screening. Almost five years after the excision, no recurrence and/or distant metastasis was observed.

Using formalin-fixed paraffin-embedded tissue samples, DNA was extracted from six sections of 10 μm thickness that included more than 80% of the cancerous area for molecular genetic testing. To detect any somatic mutations, the amplification of regions of interest was performed using a targeted multi-gene panel (Qiagen Custom Design kits, CDHS-37626Z-923), including FGFR1, BRAF, KRAS, CDK6, EGFR, SOD2, ESR1, ROS1, RICTOR, TERT, KIT, PDGFRA, PIK3CA, MYD88, ERBB4, IDH1, IDH2, ALK, STK11, ERBB2, TP53, MAP2K1, AKT1, CDK4, GAPDH, PTEN, DDR2, NTRK1, NRAS, and MET, for next-generation sequencing. The GeneReader Next-generation sequencing system (Qiagen, Germany) was used for the NGS analysis.

No germline mutation was detected. However, Next-generation sequencing analysis identified a TP53 (NM_000546.6: c.375+1G>A, pathogenic variant, TIER 1A) inactivating somatic mutation.

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. All procedures in this study involving the human participant were performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Ethical approval was not required by the local guidelines of Tekirdag Namık Kemal University for this study.

DISCUSSION

Macroscopic and microscopic features of AFX may vary.[1] Due to the absence of specific histopathological or IHC findings, it is a diagnosis of exclusion. In differential diagnosis, PDS, sarcomatoid SCC, melanoma, leiomyosarcoma, vascular tumors, reticulohistiocytoma, atypical fibrous histiocytoma, Merkel cell carcinoma, basal cell carcinoma, pseudosarcomatous dermatofibroma, and metastasis from internal malignancies should be taken into consideration.[1,3] In this case report, we illustrated the clinical, histopathological, and molecular features of a young patient with a giant AFX lesion on non-chronically sun-damaged skin.

AFX and PDS are considered a spectrum of disease.[3] Many mutations, such as the UV-dependent mutations in TP53, TERT, NOTCH1/2, and FAT1, are shared genetic abnormalities for AFX and PDS, which can explain the clinical, histopathological, immunophenotypical, and molecular relationship between the two entities.[7,8] Total excision of the tumor is necessary for differentiating AFX from PDS. The differentiation of PDS from AFX depends on the presence of at least one out of four unfavorable histological findings: coagulative necrosis, significant invasion of subcutaneous tissue, and perineural or vascular invasion.[1] No IHC or molecular method exists that can provide a definitive differential diagnosis. We diagnosed AFX based on the absence of these histological findings and because the lesion was well-defined despite the bizarre cells. We have been following the patient for 5 years and have not found any signs of recurrence and/or metastasis. Because the morphology of AFX is undifferentiated, the findings can also overlap with other undifferentiated or pleomorphic entities, such as sarcomatoid SCC and melanoma.[1,3] Comparisons of the major histopathological, IHC, and molecular features of AFX, PDS, sarcomatoid SCC, and melanoma are summarized in Table 1.

IHC is essential in the differential diagnoses, especially to exclude the two main competing considerations, sarcomatoid SCC and melanoma. Melanocytic, cytokeratin, and muscle markers are recommended IHC panels to exclude the other differential diagnoses. Additionally, CD10, vascular markers, or myocytic markers can be used.[1,3] Agaimy reported that a very strong block-type expression pattern of CD10 is highly valuable for an AFX diagnosis, whereas negative or heterogeneous patchy expression of CD10 can suggest sarcomatoid SCC or melanoma.[1]

Ultraviolet-induced (C>T or CC>TT) mutations in TP53 were reported in previous studies of AFX.[9,11] In addition, G>A somatic mutations in TP53 were reported in elderly patients with AFX lesions on the forehead as a chronically sun-damaged area.[12] Our patient had a somatic mutation in TP53 (c.375+1G>A, pathogenic variant), and the lesion site was non-chronically sun-damaged.

On the other hand, our patient had skin findings compatible with insulin resistance, yet his serum glucose level was in the normal range.[13] Diabetes and malignancy development share multiple common mechanisms, such as obesity, smoking, stress, and lifestyle. Chronic inflammation, even if low-grade, and oxidative stress can lead to an alteration in DNA structure. Insulin resistance is an independent risk factor in several solid and hematological neoplasms, as well as non-melanocytic skin tumors and melanoma.[14,15] In our patient, the association between insulin resistance and AFX development was controversial and uncertain.

Recurrence and metastasis of AFX are rare.[3,4] Recurrences usually occur within two years after excision. Especially in the case of the recurrence of completely excised AFX, the possibility of other diseases, such as melanoma or sarcomatoid SCC, should be considered.[1] In our patient, the lesion recurred within one year at the same location, probably due to an incomplete resection.

In conclusion, there is no specific marker for the definitive diagnosis of AFX. TP53 mutations can be observed in AFX, PDS, and SCC. However, the defined demarcation of the tumor, the absence of atypical mitosis and perineural/perivascular invasions, and the IHC features (strong positivity of CD10 but negativity of the others) are important in differentiating from the other

Table 1 Comparison of major histopathological, IHC, molecular, and clinical features of AFX, PDS, SSCC, and melanoma[1,3,9,10]

	AFX	PDS	Sarcomatoid SCC	Melanoma	The patient
Hx	Atypical, bizarre spindled cells,marked pleomorphism, abundant eosinophilic cytoplasm, well-circumscribed	Atypical mitosis, pleomorphic cells with vesicular nuclei and prominent nucleoli, coagulative necrosis, significant invasion of subcutaneous tissue, perineural/vascular invasion	Infiltration of dermis as single cells with elongated nuclei, no cohesive nests or islands, no/minimal signs of keratinization, spindle or pleomorphic cells are observed without clear epithelial differentiation	Highly atypical melanocytes with prominent nucleoli, cellular pleomorphism, nuclear atypia, ulceration (+/–), mitotic activity	Atypical, pleomorphic bizarre, spindled cells, well-circumscribed, encapsulated, irregular nuclei, scarce multinucleated giant cells on a keloid-like sclerotic background
IHC	CD10 (mostly strongly +) α-SMA (focal +) CD99 (mostly +) Procollagen-1 (mosty strongly +) (–) for; panCK, melanocytic, and vascular markers, desmin, and CD68	CD10 (mostly strongly +) α-SMA (focal +) PDGFRB (strongly +)	(+) for; CKs, p63, and vimentin CD10 (may be weakly + in cSCC) PDGFRB (may be strongly +) (–) for; CD99 and melanocytic markers	Melanocytic markers (+) CD10 (may be weakly +) Procollagen-1 (may be + in desmoplastic type)	CD10 strongly +
Genetics	TP53, NOTCH1/2, CDKN2A, FAT1, TERT, COL11A1, ERBB4, CSMD3	TP53, NOTCH1/2, FAT1, TERT, DNHD1, GNAS, RTN1, RTL1, ZBTB7A, NCKAP5L, FAM200A	TP53, TP63, RAS, NOTCH, CDKN2A, FAT1, and others	BRAF, NRAS, NF1, KIT, TERT, CDKN2A, and others	TP53

Hx: histopathology
IHC: immunohistochemical
AFX: atypical fibroxanthoma
PDS: pleomorphic dermal sarcoma
SCC: squamous cell carcinoma
+: positive
–: negative
+/–: positive or negative
SMA: smooth muscle actin
PDGFRB: platelet derived growth factor receptor beta
CK: cytokeratin
cSCC: cutaneous squamous cell carcinoma

doi:10.18999/nagjms.88.1.162

diseases, especially PDS. We present the case of a giant atypical recurrent AFX lesion composed of highly atypical bizarre cells to share its histopathological, IHC, and molecular features.

AUTHORS' CONTRIBUTIONS

OZ, SK, and SA conceived and designed the study. OZ and SK collected the data. OZ and SA analyzed and interpreted the results. OZ and SK wrote the manuscript. SK and SA confirm the authenticity of all the raw data. OZ contributed to manuscript drafting and critical revisions of the intellectual content. All authors have read and approved the final version of the manuscript.

COMPETING INTERESTS

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

FUNDING

No funding was received.

AVAILABILITY OF DATA AND MATERIALS

The data generated in the present study may be requested from the corresponding author.

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