Atypical fibroxanthoma and pleomorphic dermal sarcoma: A reappraisal.

Cesinaro AM, M.D., Gallo G, M.D., *Tramontozzi S, M.D., Migaldi M, M.D.

Department of Anatomic Pathology, Azienda Ospedaliero-Universitaria di Modena, Italy

*Visiting fellow from the Department of Anatomic Pathology, University "Alma Mater" of Bologna, Italy.

Dr Anna Maria Cesinaro contributed to conception and design, acquisition and interpretation of data, drafting and revising the manuscript.

Dr Graziana Gallo contributed to acquisition and interpretation of data and revising the manuscript.

Dr Sabrina Tramontozzi contributed to acquisition of data.

Dr Mario Migaldi contributed to analysis and interpretation of data.

All authors approved the final version.

Running title: AFX and PDS: A reappraisal.

Keywords: atypical fibroxanthoma; pleomorphic dermal sarcoma; histopathology; recurrence; metastasis.

Corresponding author:

Anna Maria Cesinaro M.D.

Department of Anatomic Pathology, Azienda Ospedaliero-Universitaria di Modena

Via del Pozzo 71, 41125 Modena, Italy

e-mail: cesinaro.annamaria@aou.mo.it

Phone: +39 059 4224981

Fax: +39 059 4224998

Conflict of interest and funding sources: none to disclose

Abstract

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cup.13787

Background: Atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) share clinical, pathological, immunohistochemical and molecular features, though PDS is associated with a more aggressive behavior.

Methods: We revised 71 tumors fulfilling criteria for AFX and PDS to further stratify their biological potential.

Results: Lesions predominate on the scalp of elderly men, were frequently ulcerated, one case presented necrosis, one vascular, and another perineural invasion. Fifty-one tumors were limited to reticular dermis (71.8%), 20 invaded subcutaneous tissue, focally in 13 cases (18.3%), and diffusely in seven (9.9%). A significant more frequent subcutaneous invasion was observed in tumors showing predominantly spindle compared to pleomorphic/mixed cell morphology ($p= 0.02$). At a follow-up of 17-125 months, 4 cases recurred locally, 4, 6, 10 and 13 months after surgery; no metastases were observed. Three tumors were composed of spindle cells, and one of clear cells. Three cases had margins focally involved, the fourth case had clear margins.

Conclusion: Depth of invasion and state of margins are criteria predicting prognosis in AFX/PDS; in addition, spindle cell morphology seems to be related to a more infiltrative pattern of growth and consequently aggressiveness. Grouping these tumors on a morphologic base could contribute to clarify their different biological behavior.

Keywords: atypical fibroxanthoma; pleomorphic dermal sarcoma; histopathology; recurrence; metastasis.

Introduction

Atypical fibroxanthoma (AFX) is a tumor described by Helwig in 1963[1] of still debated origin, arising on sun-exposed skin of elderly patients, with very low propensity of recurrence and almost no metastatic potential[2,3]. Pleomorphic dermal sarcoma (PDS) is a tumor with overlapping clinical, pathological and immunophenotypical features, but with referred higher recurrence rate and metastatic potential[4,5]. Recent studies found similar genetic alterations in the two neoplasms[6-8]. Both AFX and PDS are diagnoses of exclusion, to be made after careful immunohistochemical study, in order to not miss other neoplasms such as squamous cell carcinoma, melanoma, leiomyosarcoma or angiosarcoma[9].

Apart from few histologic criteria[4], it is still unclear what really differentiates these two entities. Cases of metastatic AFX have been reported[10-13], while, on the other hand, PDS indicates a category of tumors arising in the same clinical setting of AFX but showing more propensity to recur or metastasize[5]. The literature is somewhat confusing, partly because of different diagnostic criteria used by the authors[12-14], partly for incomplete immunohistochemical characterization of tumors, especially in older research[10]. In the present study, we revised clinical and pathological features, immunohistochemical profiles, and follow-up of a series of cutaneous lesions fulfilling histologic criteria of AFX and PDS. Subsequently, we focused on the histological characters related to subcutaneous invasion, in the attempt to further stratify the risk of recurrence in these cutaneous neoplasms.

Materials and methods

All skin biopsies consecutively diagnosed as AFX or sarcoma NOS, in the period 2009-2019, were retrieved from our archives. Criteria of inclusion in the study were complete clinical data, representative tumoral tissue, and immunohistochemical characterization of lesions; cutaneous involvement by sarcoma of deep soft tissue, as well as cutaneous metastases from distant sarcomas were excluded. After revision of all clinical data and slides, a total of 71 cases resulted eligible for the study. Clinical parameters were represented by patients' gender and age, anatomic site of lesions, type of surgery, and development of recurrence/metastasis.

Hematoxylin-eosin slides were reviewed, and the following features were registered: maximum diameter of tumor; type of cellular components, e.g. pleomorphic, epithelioid, spindle, other rare types; presence of ulceration, necrosis, vascular invasion, perineural invasion; infiltration beyond reticular dermis into subcutaneous tissue, subdivided in focal, when tumor focally exceeded reticular dermis, and diffuse infiltration, when tumor deeply infiltrated subcutis; state of margins. Immunohistochemical stains performed were recorded for each case, as well as the presence of any adjacent tumors.

Statistical analysis was performed by using a chi-squared test; a p value <0.05 was considered statistically significant.

Results

Clinical data of 71 cases included in the study are shown in table 1. Patients were predominantly male, and most cases developed in the seventh and eight decades. Anatomic site was the scalp in more than half of the

cases. All patients, but one lost at follow-up, underwent surgical excision *d'emblée* or incisional biopsy followed by surgical excision. Follow-up ranged between 17 and 125 months; 4 cases recurred locally, 4, 6, 10 and 13 months after surgery; after re-excision no further recurrence or metastases were observed.

Histological revision of slides demonstrated that diameter of lesions ranged between 0.3 and 12.8 cm (mean: 1.7 cm). The prevalent cell type was pleomorphic/ mixed epithelioid and spindle (37 cases) (fig. 1A), followed by predominantly spindle cell (28 cases), whereas very few cases featured epithelioid (2), clear (2), or keloidal aspect (2). Ulceration was present in 46 cases (64.7%). Vascular invasion was observed in one case (fig. 1B); necrosis was registered in another and perineural invasion in a further case. Tumors limited to reticular dermis amounted to 51 (71.8%) (fig. 1C), whereas invasion of subcutaneous tissue was observed in 20 cases, particularly 13 cases (18.3%) showed focal infiltration of adipose tissue (fig. 1D), whereas in 7 cases (9.9%) subcutaneous tissue resulted diffusely infiltrated (fig. 1E,F), with one case involving also the cranial theca. Of 37 pleomorphic/mixed cell tumors, subcutaneous tissue was infiltrated focally in 4 cases and diffusely in one case; of 28 spindle cell tumors, 8 cases infiltrated focally and 5 cases diffusely the subcutis; one case of clear cell type showed focal and one case of epithelioid type showed diffuse infiltration of adipose tissue. Dimension and ulceration did not correlate with amount of tumoral invasion, whereas we found a significant more frequent subcutaneous invasion, by considering together focal and diffuse pattern, in cases showing predominantly spindle compared to pleomorphic/mixed cell morphology ($p= 0.02$). After surgery, margins were focally involved in 7 cases. Immunohistochemical profile of tumors are shown in table 2; expression did not differ among cases with different cellular type or level of infiltration. Associated cutaneous lesions were represented mainly by actinic keratosis (26 cases), followed by squamous cell carcinoma (4) and basal cell carcinoma (1) and were found in 31 cases, with no difference related to invasiveness or cellular type of tumors.

Recurrence was observed in 4 out of 71 cases (5.6%). Specifically, none of the 51 cases limited to dermis recurred, including the case featuring perineural infiltration; recurrence occurred in one out of 13 cases showing focal infiltration of subcutis (7.7%), and in 3 of 7 cases showing diffuse infiltration (42.8%). The case showing vascular invasion, focally infiltrating adipose tissue, and the case with necrosis, also deeply infiltrating subcutis, did not recur. Statistical analysis was not performed given the low number of events. Patients with recurrent tumors were 3 males and one female. Dimensions of recurrent tumors ranged between 0.6 and 4.0 cm in diameter; two cases were localized on the scalp, one on the forehead and another on the cheek. Three tumors were composed of spindle cells, and one of clear cells. Three cases had focally involved margins, whereas margins were clear in the fourth case.

Discussion

AFX and PDS are diagnoses of exclusion and differentiation from other primary cutaneous tumors arising on sun-exposed skin, such as squamous cell carcinoma, particularly the spindle cell subtype, melanoma, leiomyosarcoma and angiosarcoma, deserves exhaustive immunohistochemistry. AFX and PDS represent a spectrum of tumors with similar histopathological, immunophenotypical, and molecular features[9,15]. Ulceration is frequently observed in both entities and does not affect tumor behavior. Our study aimed to analyze all consecutive tumors fulfilling criteria for either AFX or PDS, diagnosed during an eleven-years long period of time in our institution, therefore it was performed on routine cases, avoiding the bias of collection series or referral cases.

Analogously to previous studies, in our experience these tumors typically present as dermal based, often

ulcerated neoplasms arisen on chronically sun exposed skin, especially the scalp, of elderly people. Roughly 18% of our cases infiltrated focally and 10% diffusely the subcutaneous tissue. They demonstrated no metastatic evolution and a very low propensity to recur (5.6%) as a whole. In agreement with the current literature, recurrence occurred in those cases infiltrating the subcutis, particularly in deeply infiltrating tumors, and mostly in those with margin involvement. We did not register cases with distant metastasis, to lymph nodes or lung, as reported in few series of AFX or PDS[4,5,12,15], although our percentage of recurrence approximates that of other studies[5,15]. Interestingly, we found that spindle cell morphology was significantly more frequently associated to subcutaneous invasion, hence to recurrence, in fact three out of 4 recurrent tumors in our study were composed by spindle cells. In their paper, Wang et al. reported 11 cases of "metastatic atypical fibroxanthoma", of which at least seven infiltrating subcutis; eight cases showed spindle cell morphology, whereas the others were partly made up of spindle cells[12]. Two more cases of AFX with cutaneous or satellite metastasis have been reported[11,13]; both tumors were mainly composed of spindle cells, and at least focally infiltrated adipose tissue. These observations suggest that spindle cell morphology could be related to a more infiltrative pattern of growth and consequently aggressive behavior. This aspect has never been fully addressed in the literature. In a study of 32 PDS, Miller et al describe cases with recurrences and/or metastasis, but no correlation is made with main cellular type[4]. In a retrospective review of the literature, all reported cases of AFX with recurrences and metastases were reconsidered, focusing on their treatment and management, but the main cellular composition of tumors is not specified[16]. Another study investigated a series of undifferentiated pleomorphic sarcomas (UPS) subdivided histologically in two main groups, anaplastic/pleomorphic vs spindle/epithelioid, failing to find different behavior among the two groups[17]; nevertheless, the study included tumors not only from the head and neck, but also from the trunk and extremities, therefore it is not properly comparable to our study.

Molecular studies have failed to demonstrate alterations substantially discriminating AFX from PDS, to date[6-8], inducing some authors to consider AFX as the "not infiltrating precursor of PDS"[8]. From the immunohistochemical point of view, we did not find a different profile among tumors with different cellular types. Toll and coworkers evaluated the immunohistochemical expression of EMT (epithelial to mesenchymal transition) markers in a series of AFX and PDS, concluding that EMT does not play a role in the development of these tumors[18]. On the contrary, a more recent study found that EMT is upregulated in AFX. Since EMT is associated with progression and metastasis, the authors suggest that this could explain the recurrences or, more rarely, metastases observed in AFX and PDS[19]. Unfortunately, this study investigated a low number of cases, without indication of their follow-up. EMT has been found, also, to play a role in the sarcomatous differentiation of dermatofibrosarcoma protuberans[20], known to confer a high risk of evolution[21]. The hypothesis that EMT is upregulated particularly in tumors of the AFX/PDS group featuring spindle cell/sarcomatoid morphology, could be matter of further investigations.

In conclusion, in our experience, by strictly applying clinical, pathological and immunohistochemical criteria, few cases of AFX/PDS should be expected to recur and exceptionally to metastasize. Deepness of infiltration and type of excision proved to be robust prognostic criteria. On the other hand, our results suggest that studying these tumors grouped on a morphologic base, particularly focusing on the predominant spindle cell vs pleomorphic/mixed cell pattern, could contribute to clarifying their different biological behavior, and possibly to go beyond the definitions AFX and PDS.

References

1.Helwig EB. Atypical fibroxanthoma. Tex State J Med 1963; 59: 664-667.

2.Mentzel T, Requena L, Brenn T .Atypical Fibroxanthoma Revisited. Surg Pathol Clin 2017 Jun;10(2): 319-335.

3. Iglesias-Pena N, Lopez-Solache L, Martınez-Campayo N, Meilan-Sanchez I, Yebra-Pimentel MT, Balboa-Barreiro V, Paradela S, Fonseca E. Incidence rate and clinicopathological features of 62 atypical fibroxanthomas in a North-Western Spanish population. Australas J Dermatol 2020 Feb; 61(1): e22-e27.

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 Sep; 36(9): 1317-1326.

5. Tardio JC, Pinedo F, Aramburu JA, Suarez-Massa D, Pampin A, Requena L, Santonja C. Pleomorphic dermal sarcoma: a more aggressive neoplasm than previously estimated. J Cutan Pathol 2018 Feb; 43(2): 101-112.

6. Koelsche C, Stichel D, Griewank KG, Schrimpf D, Reuss DE, Bewerunge-Hudler M, Vokuhl C, Dinjens WNM, Petersen I, Mittelbronn M, Cuevas-Bourdier A, Buslei R, Pfister SM, Flucke U, Mechtersheimer G, Mentzel T, von Deimling A. Genome-wide methylation profiling and copy number analysis in atypical fibroxanthomas and pleomorphic dermal sarcomas indicate a similar molecular phenotype. Clin Sarcoma Res 2019 Feb 14; 9-2.

7. Griewank KG, Wiesner T, Murali R, Pischler C, Müller H, Koelsche C, Moeller I, Franklin C, Cosgarea I, Sucker A, Schadendorf D, Schaller J, Horn S, Brenn T, Mentzel T. Atypical fibroxanthoma and pleomorphic dermal sarcoma harbor frequent NOTCH1/2 and FAT1 mutations and similar DNA copy number alteration profiles. Mod Pathol 2018 Mar; 31(3): 418-428.

8. Helbig D, Ihle MA[2], Pütz K, Tantcheva-Poor I, Mauch C, Büttner R, Quaas A. Oncogene and therapeutic target analyses in atypical fibroxanthomas and pleomorphic dermal sarcomas. Oncotarget. 2016 Apr 19; 7(16): 21763-21774.

9. Ziemer M, Jaeger IM, Dippel E. Atypisches Fibroxanthoma und pleomorphes dermales Sarkom. Hautarzt. 2019 Sep; 70(9): 661-669.

10. Cooper JZ, Newman SR, Scott GA, Brown MD. Metastasizing atypical fibroxantoma (cutaneous malignant histiocytoma): report of five cases. Dermatol Surg 2005 Feb; 31(2): 221-225.

11. Lee SS, Lewis JM, Liaw K, Bushkell LL jr, Young YD, Googe PB. Recurrent atypical fibroxanthoma with satellite metastasis. J Cutan Pathol 2015 Jan; 42(1): 56-60.

12. Wang WL, Torres-Cabala C, Curry JL, Ivan D, McLemore M, Tetzlaff M, Zembowicz A, Prieto VG, Lazar AJ. Metastatic atypical fibroxanthoma: a series of 11 cases including with minimal and no subcutaneous involvement. Am J Dermatopathol 2015 Jun; 37(6): 455-461.

13. Ryan MP, Nguyen AV, Kelly BC, Raimer SS. Atypical fibroxanthoma of the scalp with cutaneous metastasis. Dermatol Surg. 2019. Sep30.

14. Davidson JS, Demsey D. Atypical Fibroxanthoma: Clinicopathologic Determinants for Recurrence and Implications for Surgical Management. J Surg Oncol 2012 May; 105(6): 559–562.

15. Brenn T. Soft Tissue Special Issue: Cutaneous Pleomorphic Spindle Cell Tumors. Head Neck Pathol. 2020 Mar; 14(1): 109-120.

16. Polcz MM, Sebaratnam DF, Fernandez-Penas P. Atypical fibroxanthoma management: recurrence, metastasis and disease-specific death. Australas J Dermatol 2018 Feb; 59(1): 10-25.

17. Winchester D, Lehman J, Tello T, Chimato N, Hocker T, Kim S, Chang J, Markey J, Yom SS, Ryan W, Mully T, Hodge D, Otley C, Arron ST. Undifferentiated pleomorphic sarcoma: factors predictive of adverse outcomes. J Am Acad Dermatol 2018 Nov; 79(5): 853-859.

18. Toll A, Gimeno J, Baró T, Hernández-Muñoz MI, Pujol RM. Study of Epithelial to Mesenchymal Transition in Atypical Fibroxanthoma and Undifferentiated Pleomorphic Sarcoma to Discern an Epithelial Origin. Am J Dermatopathol. 2016 Apr; 38(4): 270-7.

19. Lai K, Harwood CA, Purdie KJ, Proby CM, Leigh IM, Ravi N, Mully TW, Brooks L, Sandoval PM, Rosenblum MD, Arron ST. Genomic analysis of atypical fibroxanthoma. PLoS One 2017 Nov 15; 12(11): e0188272.

20. Stacchiotti S, Astolfi A, Gronchi A, Fontana A, Pantaleo MA, Negri T, Brenca M, Tazzari M, Urbini M, Indio V, Colombo C, Radaelli S, Brich S, Dei Tos AP, Casali PG, Castelli C, Dagrada GP, Pilotti S, Maestro R. Evolution of Dermatofibrosarcoma Protuberans to DFSP-Derived Fibrosarcoma: An Event Marked by Epithelial-Mesenchymal Transition-like Process and 22q Loss. Mol Cancer Res. 2016 Sep; 14(9): 820-829.

21. Erdem O, Wyatt AJ, Lin E, Wang X, Prieto VG. Dermatofibrosarcoma protuberans treated with wide local excision and followed at a cancer hospital: prognostic significance of clinicopathologic variables. Am J Dermatopathol 2012 Feb; 34(1): 24-34.

Table 1: Clinical data of 71 cases studied

Age	Gender	Anatomical site	Recurrence
<60: 1	M: 56	Scalp: 42	4 (3M/1F)
60-69: 10	F: 15	Ear: 11	
70-79:24		Cheek: 3	
80-89: 31	M/F = 3.8:1	Nose: 4	Follow-up
≥90: 5		Forehead: 5	17-125 months
		Face N.O.S.: 6	

Table 2: Immunohistochemical profile of cases studied

Antibody	clone	N# positive/total
Cytokeratin	MNF-116 (DAKO)	0/71
S-100 protein	4C4.9 (Ventana)	0/71
CD10	SP67 (Ventana)	45/45
Smooth-muscle actin	1A4 (Ventana)	21/32
CD68	PG-M1 (Ventana)	20/24
p63	4A4 (Ventana)	1 (focal)/41
p40	BC28 (Ventana)	0/10
Desmin	DER11 (Ventana)	0/39
EMA	E29 (Ventana)	0/7
CK5/6	D5/16B4 (Ventana)	0/2
CD34	QBend10 (Ventana)	0/25
CD31	JC70 (Ventana)	0/13

Legend to figure

Fig. 1 Tumor with mixed cell morphology (A, 200x, H&E); vascular invasion (arrow); the tumor, also, focally infiltrated adipose tissue and did not recur (B, H&E, 100x); tumor limited to the dermis (C, 100x, H&E); tumor with predominantly spindle cell morphology, focally infiltrating adipose tissue (D, 40x, H&E); tumor with spindle cell morphology, diffusely infiltrating subcutis (E, 40x; H&E).; the same tumor, negative for CD34 immunostaining, recurred after 10 months (F, 100x, H&E).