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Atypical fibroxanthoma and pleomorphic dermal sarcoma: Is superficial infiltration in subcutaneous tissue acceptable in AFX?

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ABSTRACT

Background: Atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) are rare cutaneous neoplasms forming a spectrum. Case reports with recurrences and metastasis have been published despite the current view that AFX is benign. The aim of this study was to identify clinical and histopathological features that predict tumor recurrence.

Methods: A retrospective review of AFX and PDS cases was performed. Clinical characteristics were obtained from patient records.

Results: A total of 29 AFX and 23 PDS cases were identified. Review led to re-classification of 12 cases (18%). In 14/50 (26.9%) cases a recurrence occurred. Recurrences were significantly more likely to occur when the tumor showed any infiltration in the subcutaneous fat (100% vs 43.2%, $p = 0.000$) or when the tumor diameter exceeded 2 cm (46.2% vs 16.2%, $p = 0.030$).

Conclusions: This study shows that histopathological distinction between AFX and PDS remains difficult with reclassification in 12 out of 52 (18%) cases upon review. All AFX cases solely confined to the dermis behaved benign. We therefore advocate to classify all cases with any form of subcutaneous extension as PDS, and only lesions without as AFX. This contrasts with the current general opinion in which superficial subcutaneous invasion is still accepted in AFX.

1. Introduction

Atypical fibroxanthoma (AFX) is a cutaneous neoplasm presenting on sun-damaged skin of the elderly, generally in the seventh and eight decades of life, with a male predilection [1,2]. It comprises up to 0.2% of all skin tumors [2]. The head and neck area, in particular the scalp, is the most affected localization. AFX and pleomorphic dermal sarcoma (PDS) share many clinical, etiologic and histopathologic features. They form a challenging diagnosis for pathologists and clinicians because of the great resemblance with a diversity of other dermatological spindle cell tumors, a lack of sensitive immunohistochemical (IHC) markers, and an unclear prognosis [2-5]. Even on a molecular level AFX and PDS are closely related and probably belong to the same disease spectrum [6-17]. Separation of these two tumors is still necessary because of the increased risk for local recurrence and even metastatic disease in PDS [1,4,18-20]. Many studies have attempted to make a better classification of these two tumors. To date, distinguishing AFX and PDS is best performed using histopathological criteria, such as subcutaneous tissue invasion, tumor necrosis and lymphovascular or perineural invasion [1,7,15,21]. But there are still no certain specific histopathological, immunohistochemic or molecular characteristics to make a definite distinction [1,15]. The main aim of this study was to determine which histopathologic features are most predictive for recurrence and prognosis.

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2. Materials and methods

In this retrospective study, biopsy and excision specimens of AFX and PDS were retrieved from the authors files. Our cohort included a total of 52 cases: 29 AFX and 23 PDS. The cases were classified based on the histopathology according to the guidelines of the World Health Organization (WHO). AFX was defined as an atypical spindled or epithelioid cell proliferation limited to the dermis in sun damaged skin, with a collarette and pushing borders and no more than minimal extension into adjacent subcutaneous tissue. The tumors lacked histopathological and immunohistochemical characteristics of a melanocytic, epithelial, smooth muscle or vascular differentiation with negativity for desmin, ERG, S100, SOX 10, and epithelial markers (panCK, CK5-6, p63). A diagnosis PDS was given to atypical spindle cell lesions that morphologically also met the criteria as mentioned in AFX, but instead showed deep subcutaneous invasion and/or presence of tumor necrosis and/or lymphovascular invasion and/or perineural growth. Clinical data including age, sex, comorbidity, previous radiotherapy or immunosuppressive therapy, clinical diagnosis, treatment, and follow-up were obtained from patient records. Histopathological parameters such as the diameter, depth, location, dominant cell type, ulceration, necrosis, mitotic rate, resection margin, vascular invasion, and perineural growth were assessed.

3. Results

The clinical data of the 52 patients are summarized in Table 2.

3.1. Cases reclassified on review

Histopathological review led to reclassification of 12 cases (18%). 11 out of the originally 40 AFX cases (27.5%) were reclassified as PDS, based on invasion beyond the superficial half of subcutaneous tissue. Of these cases, 4 turned out to be patients with recurrence(s). 1 AFX was reclassified as spindle cell squamous cell carcinoma (spSCC) showing a continuum with the atypical epidermis, positive p63 staining and weak positivity for CK5-6 and CKAE1/3.

3.2. Epidemiology, patient history and etiology

The average age of patients diagnosed with AFX was 73 years (range 58–92), and of patients diagnosed with PDS 79 years (range 61–94). 93% of the AFX tumors were male, with a male to female ratio 14:1. PDS tumors showed a similar sex distribution. AFX and PDS developed predominantly in the head and neck area (98%, 51/52), with 40 (76,9%) located on the scalp. One patient had an AFX located on the thorax. In 93% (45/48) of the AFX and PDS actinic skin damage was present. Other risk factors such as the use of immunosuppressive agents (7/52), radiation therapy (6/52), and skin trauma/scarring (1/52) were observed in our cohort but did not show any significant results. History of previous non-melanoma skin cancers was a common feature (34/52). The most suspected clinical diagnosis was squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) in 39/52 cases. Only 3 cases were clinically suspected for AFX or PDS.

3.3. Clinical features

The mean size of AFX was 13.4 mm (SD 8.9, range 3–48); for PDS this was 21.0 mm (median 16 mm, range 6–50). PDS more often exceeded a diameter of 2 cm compared to AFX (43.5% vs 10.3% respectively, $p = 0.006$). All cases of AFX presented as a solitary, nodular or polypoid, sharply demarked lesion measuring 2 cm or less in diameter. The tumors were usually pink/red or grey/beige in color. Ulceration with or without bleeding was present in 32 out of the total 52 AFX/PDS (61.5%). These clinical features weren't significantly different between AFX and PDS.

3.4. Histopathological features

On scanning magnification, AFX consisted generally of a nodular, dermal based, symmetrical tumor. Solar elastosis was present in 27/29 (93%) of the AFX cases and 22/23 (96%) of the PDS cases. The vast majority of AFX tumors were well circumscribed and showed an epidermal collarette (17/29, 58%), 12 AFX tumors showed irregular, poorly defined, or infiltrative margins.

21/29, (72%) of AFX tumors were localized in the dermis. Invasion in the upper half of the subcutis was seen in 8 (27.6%) cases. Evident perineural growth outside the tumorbulk was not observed, but in 9 of 52 (17%) AFX/PDS we saw striking presence of nerve branche(s) within the tumor. Necrosis was uncommon and seen only in 3 cases, all classified as PDS. There were no cases with vascular invasion. The cellular component of AFX and PDS was comparable. Most tumors showed highly atypical cells with pleomorphism with nuclear enlargement, hyperchromasia, and frequent mitoses. We did not find significant differences in the number of mitotic figures per 10 HPF between AFX and PDS. Limited inflammatory cells (mainly lymphocytes and macrophages) were seen in all cases typically at the periphery of the lesions. See Figs. 1–4 for representative images of AFX and PDS cases.

3.5. Immunohistochemical findings

Desmin, ERG, SOX10, CK5-6 and CK PAN AE were all negative in the 52 AFX/PDS cases. p63 showed variable mostly only focal and weak positivity in 9 AFX/PDS cases. The nuclei stained clearly less strong than in the control tissue and epidermis. In addition, none of these 9 cases showed positivity for CK PAN AE and CK 5-6. spSCC was excluded based on the absence of keratin staining in combination with the histopathological features of these 9 lesions.

3.6. Recurrences and metastases

The median length of follow-up was 51 months (range, 9–161). Two PDS showed positive surgical margins in the primary excision indicating residual disease and were excluded from the analysis. In 12/50 (24%) of AFX/PDS a recurrence occurred of which 4/29 (13.8%) patients with AFX, and 8/23 (34,5%) patients with PDS. A recurrence was defined as a recurrent tumor at or near the primary site after previous clear surgical margins. Recurrences developed within a mean time of 21.6 months (range, 1–67) after initial diagnosis. For the four AFX the mean time to recurrence was 38 months (range, 4–67) and for the 8 PDS patients 13.4 months (range, 1–34). Distant metastases were present in five cases (1 AFX (3%) and 4 PDS (17,4%). The AFX patient developed a metastasis in the soft tissue on the left side of the neck. The four PDS patients developed metastases in the lung. Recurrences were significantly more likely to occur when the tumor infiltrated the subcutaneous fat (100% vs 43.2%, $p = 0.000$), showed irregular, poorly defined, or infiltrative margins (40% vs 5%, $p = 0.006$), intratumoral nerve branches (38.5% vs 8.1%, $p = 0.010$), or when the tumor diameter exceeded 2 cm (46.2% vs 16.2%, $p = 0.030$). Case 25 (Fig. 3) demonstrates an AFX lesion which looks well-circumscribed and dermal based on low magnification. But striking are some atypical cells spreading along the fibrous septa towards the subcutaneous tissue. In our opinion this indicates a more aggressive growth pattern. This assumption is confirmed by a first recurrence that occurred 53 months after diagnosis. This patient even developed a second recurrence, which showed invasion beyond the upper half of the subcutaneous tissue, by this time clearly fitting the diagnosis PDS instead of AFX. Identical mutations in the TP53 tumor suppressor gene were found in the primary lesion and the second recurrence, indicating that it was the same tumor. We had eight similar cases with superficial extension into subcutaneous tissue. Of these eight patients, four had recurrent disease (50%). This is in contrast with zero recurrences in patients with AFX confined to the dermis (0/21). Also see Table 1 for a comprehensive overview of the most notable

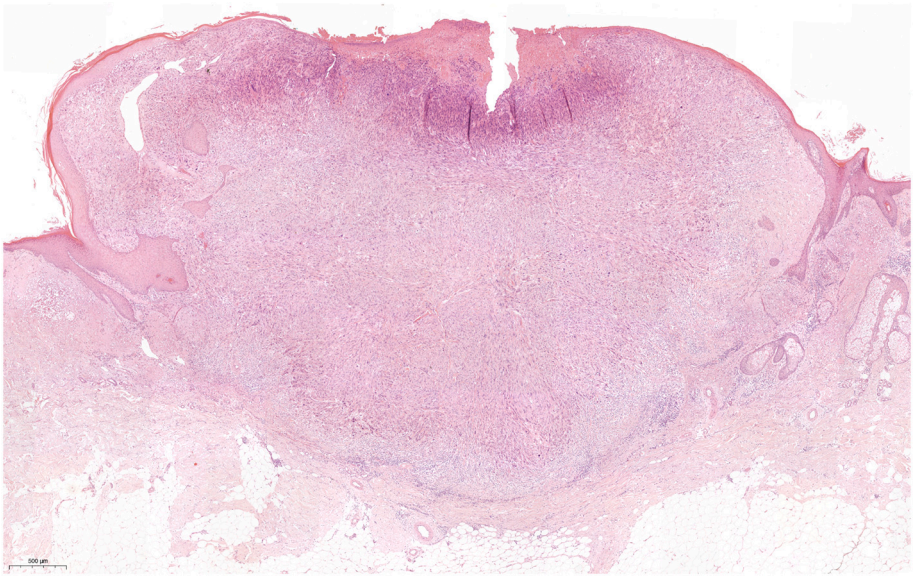

Fig. 1. Photomicrograph of an AFX tumor showing a well circumscribed lesion with pushing borders and surface ulceration (H&E, x20). The tumor is based within and confined to the dermis. This case is from a 76-year-old female (patient no 10) with an easily bleeding nodule on the right cheek, diameter of 9 mm.

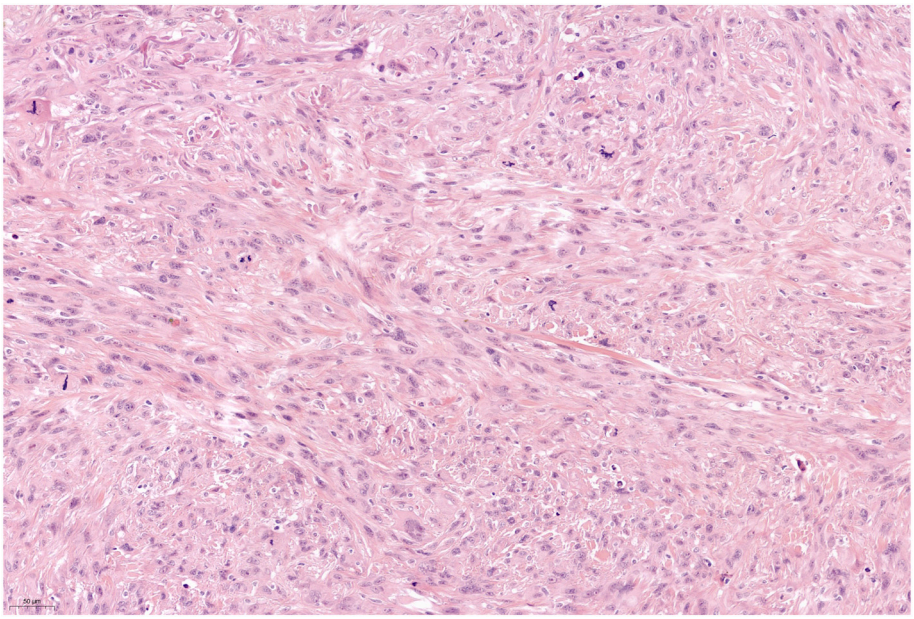

Fig. 2. Higher power showing pleomorphic spindled, and histiocytoid tumor cells. Numerous mitotic figures are seen (H&E, x200).

clinicopathological features.

4. Discussion

The aim of this study was to assess clinicopathological features that predict patient outcome in lesions within the spectrum of AFX/PDS. Our epidemiologic data, clinical and histopathological features are in line with the literature [1,2,7,12,22-24]. Upon histopathological review, in our series 11 (27.5%) out of the originally 40 AFX cases were re-classified as PDS based on subcutaneous invasion beyond the upper half of subcutaneous tissue. Four of these eleven initially wrong diagnosed AFX patients developed recurrence(s). This meets the assumption that AFX with recurrence were most likely underdiagnosed and actually represent cases of PDS [18,22,23,25,26]. Also, in our cohort recurrences were significantly (p-value = 0.000) more likely to occur when the tumor infiltrated in any extent into subcutis, even when this was focally or superficially. We found a frequency of 50% local recurrences in AFX lesions extending beyond the dermis into the underlying adipose tissue compared to none recurrence(s) in AFX lesions that were strictly confined to the dermis. This is in line with Davidson et al. who emphasized that early recurrence and invasion beyond the dermis at initial presentation are suggestive of a more aggressive clinical course. They found that AFXs extending beyond the dermis into the underlying adipose and muscular tissue had a 29.4% chance of local recurrence and an 11.8% chance of metastasis compared to lesions confined to the dermis only (9.3% and 1.8%) [4]. Wang et al. also emphasized the metastatic capacity in AFX cases with only very focal subcutaneous involvement [27]. Our results and that of Davidson et al. and Wang et al. are in contrast with the current WHO criteria and multiple studies in which infiltration into superficial subcutaneous fatty tissue is still

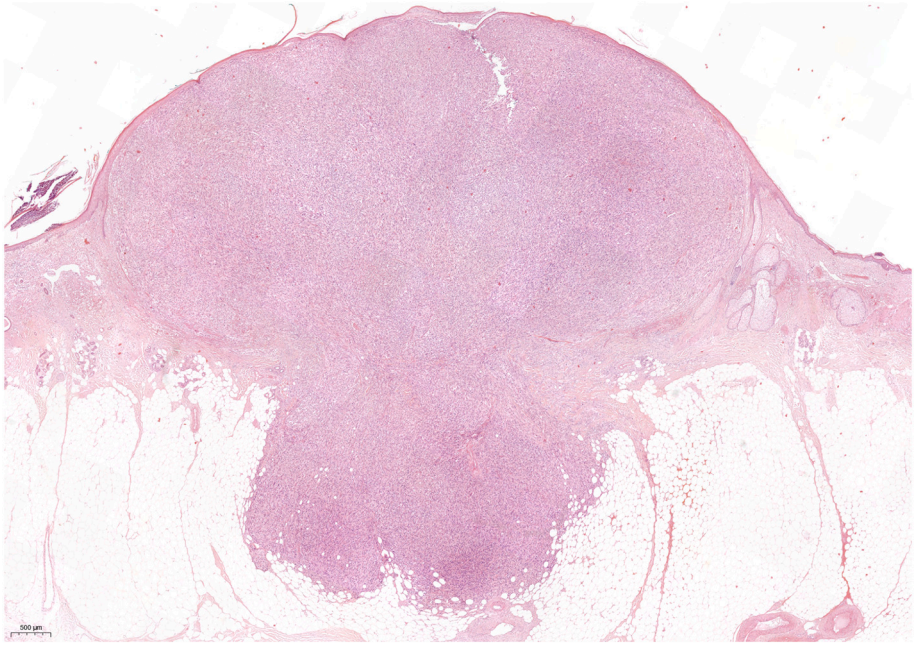

Fig. 3. Photomicrograph of a PDS tumor (H&E, x20). The tumor clearly shows deep subcutaneous extension with invasion beyond the upper half of the subcutaneous tissue. There was no perineural growth or necrosis. Four months after radical removal of this tumor a recurrence occurred. This patient (patient no 25) even developed distant metastasis in the neck area and died of the disease. This is an example of PDS without other adverse histopathological features such as necrosis and perineural growth.

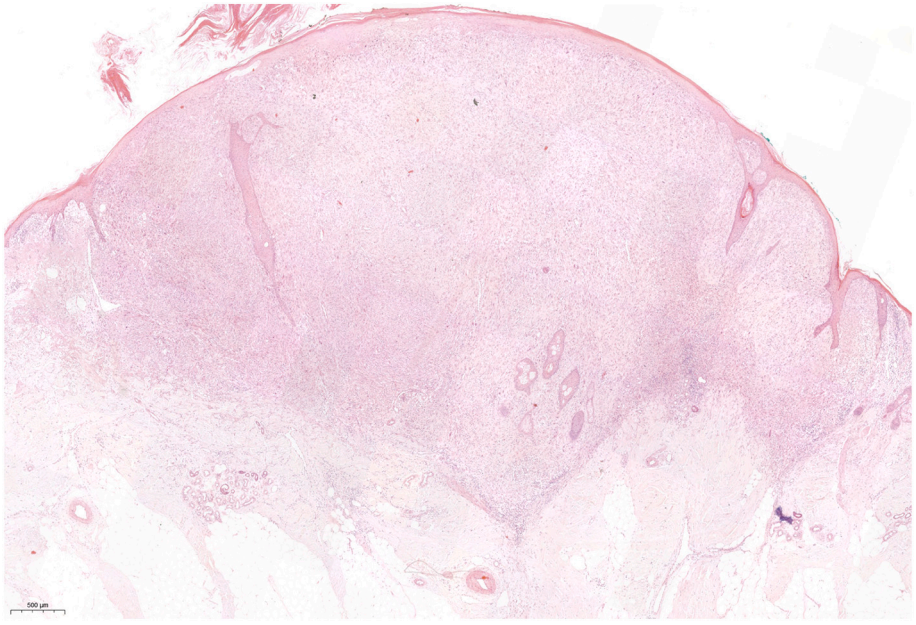

Fig. 4. Photomicrograph of an AFX tumor with a more irregular contour where tumor cells are spreading along the fibrous septa at the level of subcutaneous tissue (H&E, x20). After surgical removal, this patient (patient no 24) was diagnosed with recurrent disease some years later. This is an example of a tumor with minimal infiltration of the subcutaneous tissue, currently still accepted to fit the diagnosis of AFX. However, this kind of infiltration seems to indicate an adverse outcome.

accepted within the diagnosis of AFX [2,13,15,19,20,22,25,28]. Our data indicate to be careful and perhaps to withhold to render a diagnosis of AFX in lesions with any kind of invasive growth into the subcutaneous fatty tissue because it seems to be one of the most important determining factors for recurrence within the spectrum of AFX/PDS. This is supported by Cesinaro et al. [29].

In summary, our study shows that in daily practice still about one third of PDS cases is underdiagnosed as AFX. We demonstrate that regardless of the growing evidence that AFX and PDS are part of the same spectrum of lesions, discrimination of AFX and PDS remains important because patients develop recurrences which seems to be associated with any form of subcutaneous invasion. We therefore propose to classify only cases that are fully confined to the dermis as AFX, and to regard and treat cases with any form of subcutaneous extension as PDS.

Declaration of competing interest

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining in this study.

Appendix A

Table 1
Clinicopathological features of individual cases.

Patient no./ age, y.	Diagnosis	Ø (mm)	Diagnosis revised during study	Tumor border	Depth of invasion	Clinical outcome	Diagnosis of recurrent lesion
1/77	AFX	18	No	Circumscribed	Dermis	CR	
2/59	AFX	11	No	Circumscribed	PB	CR	
3/78	AFX	6	No	Circumscribed	Dermis	Died during FU	
4/72	AFX	3	No	Circumscribed	Dermis	CR	
5/63	AFX	27	No	Circumscribed	Dermis	CR	
6/68	AFX	25	No	Circumscribed	Dermis	CR	
7/85	AFX	16	No	Circumscribed	Dermis	CR	
8/71	AFX	8	No	Circumscribed	Dermis	CR	
9/83	AFX	9	No	Circumscribed	Dermis	CR	
10/76	AFX	9	No	Circumscribed	Dermis	CR	
11/82	AFX	17	No	Circumscribed	Dermis	CR	
12/67	AFX	12	No	Circumscribed	Dermis	CR	
13/69	AFX	11	No	Circumscribed	Dermis	CR	
14/77	AFX	10	No	Irregular	Dermis	CR	
15/64	AFX	7	No	Circumscribed	Dermis	CR	
16/58	AFX	9	No	Irregular	Dermis	CR	
17/86	AFX	48	No	Irregular	Dermis	Died during FU	
18/78	AFX	10	No	Circumscribed	Dermis	CR	
19/92	AFX	–	No	Irregular	Dermis	CR	
20/78	AFX	18	No	Irregular	Dermis	CR	
21/79	AFX	15	No	Circumscribed	Upper half SC	CR	
22/69	AFX	7	No	Circumscribed	Dermis	CR	
23/60	AFX	17	No	Infiltrative	Upper half SC	Recurrence after 21 mo	AFX (with infiltration in upper half of SC)
24/74	AFX	14	No	Infiltrative	Upper half SC	Recurrence after 53 mo	AFX (with infiltration in upper half of SC)
25/64	AFX	20	No	Infiltrative	Upper half SC	Recurrence after 4 mo. Neck metastasis after 8 mo	PDS
26/75	AFX	11	No	Infiltrative	Upper half SC	CR	
27/68	AFX	10	No	Infiltrative	Upper half SC	CR	
28/72	AFX	8	No	Infiltrative	Upper half SC	CR	
29/76	AFX	12	No	Infiltrative	Upper half SC	Recurrence after 45 mo	PDS
30/84	PDS	8	Yes – AFX to PDS	Circumscribed	Deep subcutis	CR	
31/91	PDS	14	Yes – AFX to PDS	Circumscribed	Deep subcutis	CR	
32/84	PDS	12	Yes – AFX to PDS	Circumscribed	Deep subcutis	Recurrence after 12 mo	AFX (well circumscribed dermal lesion)
33/94	PDS	15	Yes – spSCC to PDS	Infiltrative	Deep subcutis	CR	
34/76	PDS	18	Yes – AFX to PDS	Infiltrative	Deep subcutis	CR	
35/78	PDS	22	Yes – AFX to PDS	Infiltrative	Deep subcutis	Recurrence after 10 mo, Lung metastasis after 9 mo	PDS
36/76	PDS	14	Yes – AFX to PDS	Infiltrative	Deep subcutis	CR	
37/82	PDS	9	Yes – AFX to PDS	Infiltrative	Deep subcutis	CR	
38/75	PDS	25	Yes – AFX to PDS	Infiltrative	Deep subcutis	Recurrence after 34 mo	AFX (with infiltration in upper half of SC)
39/85	PDS	10	Yes – AFX to PDS	Infiltrative	Deep subcutis	CR	
40/61	PDS	16	No	Infiltrative	Deep subcutis	Recurrence after 13 mo, Lung metastasis after 36 mo.	PDS
41/67	PDS	32	No	Infiltrative	Deep subcutis	Lung metastasis after 16 mo	PDS
42/79	PDS	25	No	Infiltrative	Deep subcutis	CR	
43/82	PDS	45	No	Infiltrative	Deep subcutis	CR	
44/81	PDS	6	No	Infiltrative	Deep subcutis	CR	
45/64	PDS	50	No	Infiltrative	Deep subcutis	Recurrence after 3 weeks	PDS
46/89	PDS	37	Yes – AFX to PDS	Infiltrative	Deep subcutis	CR	
47/77	PDS	28	No	Infiltrative	Deep subcutis	Recurrence after 10 mo	PDS
48/70	PDS	15	No	Infiltrative	Deep subcutis	Recurrence after 8 mo	PDS
49/93	PDS	40	No	Infiltrative	Deep subcutis	Positive surgical margins, Died during FU	
50/79	PDS	13	No	Infiltrative	Deep subcutis	CR	
51/82	PDS	29	No	Infiltrative	Perichondrium	Recurrence after 16 mo, Lung metastasis after 20 mo	PDS
52/69	PDS	7	No	Infiltrative	Deep subcutis	Positive surgical margins with persistent disease.	PDS

Abbreviations: No, number; y, years; AFX, atypical fibroxanthoma; PDS, pleomorphic dermal sarcoma; spSCC, spindle cell squamous cell carcinoma; PB, pushing border into subcutis; SC, subcutaneous tissue; FU, follow-up; Ø, tumor diameter; CR, complete remission; mo, months; LN, lymph node.

Table 2
Patient characteristics after histopathological review and reclassification.

	AFX		PDS		Total cohort	
Variables	n	%	n	%	n	%
Total number of patients	29	55.8%	23	44.2%	52	100%
Mean age (range)	73 years (58–92)		79 years (61–94)		76 years (58–94)	
Sex						
Female	2	6.9%	2	8.7%	4	7.7
Male	27	93.1%	21	91.3%	48	92,3
Tumor diameter						
Mean (range)	13.4 mm (3–48)		21.0 mm (6–50)		17.1 mm (3–50)	
<2.0 cm	26	89.7%	13	56.5%	29	55.7
≥2.0 cm	3	10.3%	10	43.5%	23	44.2
Ulceration						
No	11	37.9%	9	39.1%	20	38.5
Yes	18	62.1%	14	60.9%	32	61.5
Necrosis						
No	29	100%	20	87%	49	94.2
Yes	0	0%	3	13%	3	5.8
Lymphovascular invasion						
No	29	100%	23	100%	52	100
Yes	0	0%	0	0%	0	0%
Perineural invasion						
No	29	100%	14	60.9%	43	82.7
Yes	0	0%	9	39.1%	9	17.3
Invasion level						
Dermal based	19	65.5%	0	0%	19	36.5
Pushing border into subcutaneous tissue	2	6.9%	0	0%	2	3.8
Superficial subcutis	8	27.6%	0	0%	8	15.4
Deep subcutaneous tissue	0	0%	23	100%	23	44.2
Recurrence						
Yes	4	13.8%	10	43.5%	14	26.9%
No	25	86.2%	12	52.2%	37	71.2%
Mean time to recurrence (range)	38 months (4–67)		13.4 months (1–34)		21.6 months (1–67)	
Mean duration of follow up (range)	63.9 months (9–133)		54.3 months (12–161)		51 months (9–161)	

Abbreviations: n, number; AFX, atypical fibroxanthoma; PDS, pleomorphic dermal sarcoma.

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