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S1-guideline atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS)

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Doris Helbig[1]*, Mirjana Ziemer[2]*, Edgar Dippel[3], Michael Erdmann[4], Uwe Hillen[5], Ulrike Leiter[6], Thomas Mentzel[7], Georg Osterhoff[8], Selma Ugurel[9], Jochen Utikal[10], Dagmar von Bubnoff[11], Carsten Weishaupt[12], Stephan Grabbe[13]

(1) Department of Dermatology and Venereology, University Hospital Cologne, Germany
(2) Department of Dermatology, Venereology, and Allergology, University Hospital Leipzig, Germany
(3) Department of Dermatology and Venereology, University Hospital Ludwigshafen, Germany
(4) Department of Dermatology, University Hospital Erlangen, Comprehensive Cancer Center Erlangen – European Metropolis Region Nürnberg, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany
(5) Department of Dermatology and Venereology, Vivantes Klinikum Berlin Neukölln, Berlin, Germany
(6) Center for Dermato-Oncology, University Hospital Dermatology, Eberhard-Karls-Universität Tübingen, Germany
(7) MVZ Dermatopathology Friedrichshafen, Bodensee, Germany
(8) Department and Clinic for Orthopedics, Trauma Surgery, and Plastic Surgery, University Hospital Leipzig AöR, Germany
(9) Department of Dermatology, Venereology, and Allergology, University Hospital Essen, Germany
(10) Clinical Cooperation Unit Dermatology of the German Cancer Research Institute Heidelberg (DKFZ) and the Department of Dermatology, Venereology, and Allergology, Medical Faculty Mannheim, Ruprecht-Karls-Universität Heidelberg, Germany
(11) Department of Dermatology, Venereology, and Allergology, University Hospital Schleswig-Holstein, Campus Lübeck, Germany
(12) Department of Skin Diseases, University Hospital Münster, Germany
(13) Department of Dermatology, University Hospital, Johannes Gutenberg University Mainz, Germany

* Both authors contributed equally to this work.

Summary

Atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) are rare cutaneous neoplasms representing histomorphological, genetic as well as epigenetic variants of a disease spectrum. Both tumors typically manifest as nonspecific, often ulcerated, skin- to flesh-colored nodules in chronically sun-damaged skin of elderly male patients. AFX is a rather well demarcated, often rapidly growing tumor. PDS tumors

are poorly circumscribed and are characterized by aggressive infiltrative growth. Fast as well as slow growth behavior has been reported for both tumors. Histologically, both are composed of spindle-shaped and epithelioid tumor cells with pleomorphic nuclei as well as atypical multinucleated giant cells. Atypical mitoses are common. In contrast to AFX, PDS involves relevant parts of the subcutis and shows areas of tumor necrosis and/or perineural infiltration. Due to the poorly differentiated nature of AFX/PDS (Grade 3), histopathologically similar cutaneous sarcomas, undifferentiated carcinomas, melanomas and other diseases have to be excluded by immunohistochemical analysis.

The treatment of choice is micrographically controlled surgery. In cases of AFX, a cure can be assumed after complete excision. Local recurrence rates are low as long as PDS tumors are surgically removed with a safety margin of 2 cm. Metastasis is rare and mostly associated with very thick or incompletely excised tumors; it mainly affects the skin and lymph nodes. Distant metastasis is even more rare. No approved and effective systemic therapy has been established.

1. Epidemiology, etiology, and clinical appearance

Atypical fibroxanthoma (AFX: ICD-10 D48.5, ICD-O 8830/1) and pleomorphic dermal sarcoma (PDS: ICD-10 C49, ICD-O 8802/3) are rare cutaneous neoplasms [1]. There are no detailed data on incidence.

AFX was first described by Helwig in the nineteen-sixties [2]. He described them as tumors occurring mainly on the face and scalp, with frequent ulcerations. Helwig assumed a fibroblastic origin and described the histological characteristics as a quite clearly circumscribed infiltration of the dermis by pleomorphic spindle cells, polynuclear atypical giant cells and mitoses. He was unable to determine the dignity of AFX but noted that the clinical course appeared to be "benign". Soon after, Kempson et al. confirmed this assessment but assumed a reactive or reparative process [3]. Even at the time of the first description, there were doubts about the homogeneity of the cases, since with histopathology they might appear as fibrosarcomas, leiomyosarcomas, rhabdomyosarcomas, undifferentiated carcinomas or melanomas [2, 3]. According to interobserver assessment, reticulohistiocytomas, myofibrosarcomas, leiomyosarcomas and pseudosarcomatous dermatofibromas have frequently been misdiagnosed as AFX [4]. It was initially suspected that AFX/PDS might constitute a superficial variant of histomorphologically similar tumors of the soft tissues in deeper subfascial layers (malignant fibrous histiocytoma (MFH), nowadays called undifferentiated pleomorphic sarcoma or UPS). This suspicion was later disproved. On the one hand, MFH was a term for a number of poorly differentiated malignant neoplasms that can now be clearly categorized into individual diagnoses such as dedifferentiated liposarcomas, leiomyosarcomas, rhabdomyosarcomas, and other entities (such as malignant solitary fibrous tumors) with immunohistochemistry and electron microscopy. On the other hand, the term MFH was also used for a group of discrete undifferentiated soft tissue sarcomas [USTS] [5]. The latter do not show any line differentiation that can be detected with current methods. UPS is a variant of USTS. Terms like 'superficial MFH' or 'dermal UPS', formerly used for AFX/PDS, are obsolete. The term 'PDS' is used for tumors histomorphologically corresponding to AFX but involving significant parts of the subcutis and/or showing necrotic areas and/or perineural or lymphovascular spreading. Based on the similarities of clinical appearance, histology and molecular genetics (genetics and epigenetics), the current view is that AFX and PDS represent a spectrum of a single entity [5–11].

Fibroblastic, myofibroblastic, or "histiocytic" line differentiation for AFX/PDS was discussed for decades [12–15]. Risk factors described for AFX/PDS, such as UV exposure, ionizing radiation, immunosuppression, and xeroderma pigmentosum as well as molecular alterations of the tumor cells led to the hypothesis that AFX and PDS might correspond to dedifferentiated squamous cell carcinomas [10]. In addition, histomorphological arguments like (in some cases) the detection of intercellular bridges as an indication of epithelial differentiation, as well as ultrastructural evidence of tonofilaments and desmosome-like structures, indicated a connection with cutaneous squamous cell carcinomas (cSCCs) [16]. AFX/PDS is negative for keratin, but this does not exclude keratin differentiation since we know that dedifferentiated variants of malignant neoplasms in internal organs are able to convert from a keratin-positive/vimentin-negative profile to an inverse profile [17]. In one current publication, PDS could be clearly separated from well-differentiated to poorly

differentiated cutaneous SCC with based on transcriptomic data. In addition, differential gene expression analyses of PDS and cutaneous SCC indicate a mesenchymal (fibroblastic) line differentiation of PDS [18]. In the 2020 WHO classification, AFX and PDS are still listed in the chapter "*Tumors of uncertain differentiation*" [19].

Clinical appearance is non-specific. AFX and PDS are typically found in areas chronically exposed to sunlight, most frequently on the scalp and more rarely in other areas such as the lower arms or backs of the hands. The tumors are skin- to flesh-colored, sometimes indurated, and are frequently in the form of ulcerated nodes that can grow up to several centimeters in size. The surrounding skin usually shows signs of chronic sun damage. AFX is usually clearly circumscribed, while PDS may show less clear demarcation and frequently more aggressive, infiltrating growth. Tumor growth varies between a few weeks and several months, with PDS often developing over longer periods of time. Most of the patients have additional skin tumors in areas with chronic sun damage, such as actinic keratosis, basal cell carcinoma, or squamous cell carcinoma [21, 41], frequently in close vicinity to the area of their AFX/PDS (field cancerization). The age peak at diagnosis is in the 7th to 8th decade of life; men are affected about eight times as frequently as women [20]. These tumors may occur at a younger age in patients with immunosuppression or genetic predisposition with mutations in tumor suppressor genes or gene repair enzymes.

2. Diagnostics

2.1. Histology

Diagnosis of AFX and PDS is based on the histology as an exclusion diagnosis. The tumor usually borders directly on the epidermis; in some cases a narrow "grenz zone" may separate the tumor from the epidermis. Tumor cells show various morphologies with atypical spindle-shaped and epithelioid cells with pleomorphic, vesicular, or hyperchromatic nuclei as well as atypical polynuclear giant cells and often atypical mitoses. These are limited to the dermis in AFX (without any significant infiltration of fatty tissue), while in PDS, substantial parts of the subcutaneous fatty tissue or other deeper structures are affected. Differentiation between AFX and PDS is therefore not possible with a superficial biopsy. Deep spindle biopsy is required for a definite diagnosis.

Classic AFX is usually an exophytic, clearly circumscribed tumor, in many cases with central ulceration, surrounded by a "collar" of hyperplastic epidermis. There are rare variants including spindle cell, myxoid, clear cell, granular cell, pseudoangiomatous, pigmented, or sclerosing AFX as well as AFX with regressive alterations, with keloid-like hyalinization, and AFX with numerous osteoclast-like giant cells [21, 22]. In contrast, PDS is less clearly demarcated with more aggressively infiltrating neoplasms and invasion of the subcutis, the skeletal muscles, and/or fascial tissues. They may also display tumor necroses, lymphovascular infiltration, and/or perineural infiltration. This is not the case with AFX. The tumoral stroma may show myxoid, desmoplastic, or keloid changes. A more aggressive clinical course has been associated with infiltration of deeper tissues, lymphovascular or perineural invasion and necrotic areas [22–26].

Due to the non-specific histology, other tumors such as dedifferentiated cutaneous SCC, melanoma, vascular tumors and other sarcomas, as well as reticulohistiocytoma and atypical fibrous histiocytoma must be excluded with immunohistochemistry before a diagnosis of AFX/PDS is made [21]. For exclusion of the differential diagnoses, an immunohistochemistry panel of at least two melanocytic markers (such as S100, Sox10), two cytokeratin markers (such as AE1/3, MNF116, KL1, or CAM5.2), and one muscle marker (desmin) is recommended. This may be augmented as necessary by using additional markers such as CD10, a vascular marker (CD34, ERG) or other myocytic markers (alpha smooth muscle actin, α-SMA) [22, 27, 28].

One study showed that pleomorphic dermal sarcomas were 100 % positive with immunohistochemical staining for PDGFRB, while cutaneous SCCs, even dedifferentiated cSCCs, were 100 % PDGFRB-negative [18]. Another study also found strong expression of PDGFRB in tumor cells from advanced SCC [29].

Apart from CD10, a relatively large proportion of AFX/PDS is positive for CD99 and procollagen-1 [23, 30–35] (Table 1). Alpha-SMA and CD68 may show focal positivity [23, 30–34]. TP53 is expressed in a majority of cases due to *TP53* mutations leading to a non-functional TP53 protein [8, 9]. When using melanocytic markers, it should be remembered that nuclear expression of MiTF may be present, and in very rare cases the tumors may also be Melan-A or HMB45 positive. Isolated use of these melanocytic markers should therefore be avoided [36–38]. The tumors may also express CD31 (in 41 %), and this should be considered with differential diagnosis [39].

2.2. Genetic alterations and immune phenotyping

Due to their similarities in UV-dependent genetic mutations, AFX and PDS are now considered a spectrum of a single entity. Both display a very high mutation load (on average 42.7 mutations per megabase in PDS). This is even higher than in cSCC and melanoma [18]. Pleomorphic dermal sarcomas display the UV-induced mutational signatures 7a und 7b in nearly equal portions, while other UV-induced tumors such as

Table 1 Use of immunohistochemical markers for diagnosis of atypical fibroxanthomas (AFX) and pleomorphic dermal sarcomas (PDS).

Markers	Staining properties
Routine markers (mandatory)	
Pancytokeratin markers (AE1/3, KL1, CAM5.2)	AFX/PDS negative
Melanocyte markers (S100, Sox10)	AFX/PDS nearly always negative
Desmin	AFX/PDS negative
CD34/ERG	AFX/PDS negative
Additional markers (facultative)	
CD10	Most tumor cells are strongly positive with AFX/PDS, but weakly positive in 50 % of cutaneous SCC and expressed in 33 % of MM
α-SMA	Focal positivity common in AFX/PDS
PDGFRB	PDS positive in 100 %, but strong positivity may also be seen in advanced SCC
CD99	AFX mostly positive, negative in cutaneous SCC, 10 % positive in MM
Procollagen-1	AFX mostly strongly positive, rarely reactive in cutaneous SCC, weak to moderate expression in about one-third of desmoplastic MM
CD68 or Ki-M1p	Rarely positive macrophages, tumor cells mostly negative

cSCC, basal cell carcinoma and melanoma typically show the 7a signature and only rarely 7b. Signature 44, which has been associated with a defective DNA mismatch repair (MMR), can be detected in a small number of PDS (3 out of 28), but is much more common in cSCC [18].

The most common genetic alterations include *TP53*-loss-of-function mutations, which can be detected in all AFX/PDS, followed by alterations in the *CDKN2A/B* gene (*CDKN2A/B* mutations in 68 %, deletions in 71 %, and both in 46 %) [18]. Other common mutations include *DNHD1, GNAS, RTN1, RTL1, ZBTB7A, NCKAP5L, FAM200A*, *NOTCH1/2* and *FAT1* as well as TERT promoter mutations [6-8, 13, 15, 18]. Deletions in the *CDKN2A/B* gene as well as amplifications in the *TRAPP12* and *PDGFRA/KIT* gene have been detected [18] (Table 2).

Immunohistochemical and mRNA expression analyses of the immune microenvironment have shown that the majority of PDSs are in fact inflammatory and immunogenic tumors with a large number of CD8-positive tumor-infiltrating lymphocytes (TILs) and expression of various checkpoint molecules such as PD-L1, TIGIT, LAG-3, and CTLA-4 [18, 43, 44]. These results indicate that PDSs, particularly those with a high number of infiltrating CD8-positive lymphocytes, PD-L1 und LAG-3 expression as well as MHC-I and –II expression, may induce an adequate antitumor immune response that might be improved with immune checkpoint inhibitors. Only a small proportion of the tumors appears to develop immune escape mechanisms such as down-regulation of MHC-I molecules (in 2 out of 28 tumors) [18, 43, 44].

2.3. Dermoscopy and other methods of in-vivo imaging

Currently, dermoscopy, confocal laser scanning microscopy, and optical coherence tomography have only limited significance in the diagnostics of AFX and PDS. In 2018, the International Dermoscopy Society described the dermoscopic properties of 40 AFX. The overwhelming majority showed red and white structureless areas, and slightly less than half showed irregular linear vessels. In comparison with basal cell carcinoma, none of the dermoscopic criteria achieved statistical significance. However, in comparison with squamous cell carcinomas, three variables (red structureless areas, lack of opaque yellowish-white scaling, and lack of so-called white circles) were statistically significant in predicting AFX [45].

There are hardly any studies of modern in-vivo imaging methods such as optical coherence tomography or multiphoton laser tomography with AFX or PDS. Only one recent publication describes the in-vivo and ex-vivo confocal characteristics of AFX [46].

Locoregional lymph node sonography should be performed in patients with PDS if locoregional metastasizing is suspected or detected. In cases of non-movable tumors or suspected deep infiltration, locoregional cross-sectional imaging is indicated [47–49].

Table 2 Molecular genetic alterations of AFX/PDS and cSCC (the works cited are based on various approaches and techniques, including some that are outdated. The number of samples studied is often very small: the results of the studies are therefore not directly comparable).

	AFX/PDS	SCC
Mutations	– *TP53* [6, 8, 9, 14, 18] – *NOTCH1/NOTCH2* [6, 18] – *CDKN2A/B* [6, 18] – *FAT1* [6, 18] – *DNHD1, GNAS, RTN1, RTL1, ZBTB7A, NCKAP5L, FAM200A* [18] – *TERT promoters* [6, 7] – *COL11A1, ERBB4, CSMD3* [13] – Rarely *HRAS, KRAS, NRAS* [15, 18]	– *TP53* [18, 40–42] – *NOTCH1/NOTCH2* [18, 40–42] – *CDKN2A* [18, 40–42] – *FAT1, RASA1* [42] – Rarely *PIK3CA, FGFR3, BRAF, HRAS, EGFR, KIT* [41, 42]
Copy Number Variations	Loss: – *9p, 13q* [10, 13] – *CDKN2A/B deletions* [8, 10, 13, 18] – *8p23.3-4 deletion* [18] Amplifications: – *8q* [10, 13] – *2p25.3 (TRAPP12)* amplification [18] – *PDGFRA/KIT amplification* [18]	Loss: – 3p, 9p (CDKN2A), 13q [10] Amplifications: – 3q, 8q [10] – 8q24.21 (MYC) amplifications [10] – 11q13.3 (CCND1) amplifications [10]

3. Prognosis and staging

The prognosis of AFX and PDS depends on vertical spreading, infiltration of deeper tissues such as the subcutaneous fatty tissue and fascia, as well as perineural or vascular invasion.

Curative success can be expected after complete excision of AFX [50, 51]. With R0 resection, the rate of local recurrence is less than 5 % [50, 51]. A meta-analysis of numerous studies with a total of 907 patients with AFX showed that those treated with micrographically controlled surgery had lower recurrence rates than those treated with conventional surgery using wide clinical safety margins [52]. Metastasizing of AFX has not been reported in the current literature. Older reports of metastasizing were published at a time when immunohistochemical markers were not available, so they may not refer to AFX/PDS at all and will not be considered in this context.

For PDS with evidence of relevant infiltration of subcutaneous or deeper tissues, locoregional recurrence was reported in 5–28 % of cases [20, 25, 53], mostly occurring within two years after primary excision. However, the majority of these recurrences resulted from incomplete resection [25, 50]. In a retrospective study with 92 PDS patients, a safety margin of 2 cm was associated with a lower risk of local recurrence [20]. Metastasizing is not uncommon with PDS, with an increased risk in cases of very thick primary tumors with infiltration of deeper tissues, and in cases of incomplete resection. Metastases usually spread into the skin and regional lymph nodes; remote metastases are rarer. Rates of metastasis in PDS are estimated to be between 8.8 % and 20 % [20, 25, 53]. In one study of 32 cases of PDS, 29 patients were followed up. Metastases were found in three patients (10 %); in two cases into the skin and in one case into the regional lymph nodes. Only one patient (3.4 %) with underlying hemato-oncological disease developed remote metastases [25]. In a retrospective analysis of 18 PDS cases, 15 patients were followed up. Three patients (20 %) developed metastases into the skin, regional lymph nodes and the lung. These were those patients from the cohort who had the thickest primary tumors infiltrating into the skeletal muscles or at least the fascia [53]. In the most recent retrospective study with 92 PDS patients, 19.6 % of patients developed local recurrence or skin metastases, 3.3 % had lymph node metastases, and 5.4 % had metastases in the lungs. Two of the three patients with lung metastases had underlying hemato-oncological disease. Viewing all published case cohort studies together, rates of metastasis into internal organs appear to be between 4 % and 10 %, mostly in patients with underlying hemato-oncological disease [20, 25, 53].

4. Treatment

4.1. Surgery

Both AFX and PDS should be treated with curative intent and radical excision with subsequent histopathological examination. If possible, excision should be performed with micrographic margin control and an adequate safety margin (Table 3), since local recurrence usually results from incomplete resection [20, 55]. The final decision to deviate from these safety margins should be taken by the surgeon together with the patient after careful explanation, depending on the site of the tumor. PDS tumors are rare and should be discussed with an interdisciplinary skin tumor board regardless of stage. The safety margin for PDS should be widened to about 2 cm to decrease the risk of local recurrence (anatomical, functional, and esthetic aspects should of course be taken into account) [20, 52, 54, 55]. With AFX, micrographically controlled excision with a narrow safety margin appears to be sufficient.

4.2. Radiation therapy

There are no published data on the radiation sensitivity of AFX/PDS. If complete resection is not feasible, subsequent irradiation of the tumor area may be considered. The efficacy of adjuvant irradiation on the prognosis of completely excised PDS has not been sufficiently investigated. However, there was a positive but non-significant trend towards fewer local recurrences or metastases in one analysis of a small number of patients who received adjuvant irradiation [20].

Table 3 Safety margin for primary excision.

Type	Safety Margin
AFX	Micrographically controlled surgery (MCS) or clinical safety margin of at least 0.5 cm
PDS	Broad safety margin, if possible 2 cm with MCS; safety margin may be adapted to the anatomical situation if required

4.3. Medical therapy

There is no effective systemic standard treatment for AFX/PDS. Treatment recommendations for inoperable patients or metastasized PDS (frequently very old and multimorbid patients) should be discussed with an interdisciplinary tumor board. Molecular genetic investigations, mutation burden, PD-L1 expression and detection of tumor-infiltrating lymphocytes (TILs) may be considered in individual treatment decisions. There are only a few individual case reports on experimental treatments with chemotherapies such as doxorubicin, ifosfamide combined with doxorubicin or electrochemotherapy [25, 56, 57].

In cases with high numbers of TIL and expression of PD-L1 or other checkpoint molecules, off-label treatment with a checkpoint inhibitor such as an anti-PD-1 antibody may be considered, provided that the reimbursement situation has been clarified. There are some case reports that PD-1/PD-L1 inhibiting antibodies may be effective [18, 43, 44, 58].

Targeted therapies may be used if oncogenic changes are detected, but there is currently no experience with targeted therapies for AFX/PDS [8, 9, 18].

5. Follow-up

There is no evidence regarding systematic follow-up of patients with AFX and PDS. The aim is early detection of local recurrence as well as lymph node and remote metastases. Examinations every six months for AFX and every three months for PDS in the first two years are recommended, then every year for AFX and every six months for PDS thereafter for at least five years. A schedule for follow-up is presented in Table 4.

For PDS, clinical examination should include palpation of the regional lymph nodes based on the abovementioned risk of recurrence and metastasis. In the first five years, PDS patients should have an ultrasound examination of the primary tumor region and regional lymph nodes. Additional instrumental diagnostics such as CT or MRI cross-sectional imaging may be indicated for cases of pathological

Table 4 Suggestion for follow-up care at risk-adapted intervals.

	AFX		PDS		Recurrent tumors or tumors with locoregional, lymph node, or remote metastasis
Year	1–2	3–5	1–2	3–5	1–5
Clinical follow-up (months)	6	12	3	6	As required
Ultrasound of scar and regional lymph nodes	–	–	6	6	As required
Cross-sectional imaging	–	–	–	–	As required

ultrasound, special primary tumors (for example with vascular invasion), recurrence or metastasized tumors (Table 4).

6. Procedures for consensus building

This updated version of the guideline was commissioned by the Working Group Dermatological Oncology (ADO) of the German Cancer Society (DKG) and the German Dermatological Society (DDG)

The most important recommendations of this guideline are summarized in Table 5. With regard to conflicts of interest, experts with a possible conflict of interest did not participate in formulating recommendations on the relevant topics. Assessment of conflicts of interest for the individual experts was performed by the guideline coordinators; the coordinators themselves were assessed by the authorized guideline representative for ADO/DKG.

Guideline coordinators: PD Dr. med. Doris Helbig, Cologne; PD Dr. med. Mirjana Ziemer, Leipzig

Authorized guideline representative for ADO/DKG: Prof. Dr. med. Stephan Grabbe, Mainz

Table 5 Overview of the most important statements and recommendations of the S1 guideline AFX and PDS (as of 2021).

Topic	Statement/Recommendation of the guideline
Entity	AFX and PDS are two conditions within the spectrum of the same tumor entity
Dignity and growth	AFX: < 5 % recurrence (after R0 resection); no metastases PDS: 5–28 % recurrence (although most topical recurrences were due to insufficient resection of the tumor); metastases in about 9–20 % of cases, mainly skin and lymph nodes; remote metastases are rare, occurring mainly in the lungs and mostly in patients with underlying hemato-oncological disease.
Epidemiology	Rare skin neoplasms (exact incidence unknown), affecting mostly men in their 7th or 8th decade of life.
Clinical appearance	AFX and PDS usually present as painless, in some cases ulcerated nodes with a diameter of up to several centimeters in areas with chronic UV exposure (head and neck).
Diagnostics	Excision and histopathology: atypical, spindle-shaped/epithelioid tumor cells with pleomorphic nuclei, in part with polynucleated giant cells and frequently atypical mitoses. In AFX, this is limited to the dermis, while PDS affects significant portions of the subcutaneous fatty tissue or other deep tissues (NOTE: Superficial biopsies cannot be used to differentiate between AFX and PDS!). PDS may also show additional lymphovascular and/or perineural invasion and/or necrosis. Diagnosis is made after exclusion of other spindle cell tumors. Locoregional lymph node sonography is indicated in cases of PDS, or if locoregional spreading is suspected or detected. Locoregional cross-sectional imaging is indicated in cases of non-movable tumors or suspected deep infiltration.
Prognostic factors	The prognosis for PDS is worse than for AFX. R1 or R0 resection without a safety margin has a poor prognosis, as has underlying hemato-oncological disease (impaired immune response)
Surgical treatment	Complete excision of the tumor is the goal, if possible with three-dimensional micrographic margin control: for AFX with a narrow safety margin, for PDS with a “wide” safety margin (up to 2 cm if anatomically feasible while avoiding functional or esthetic impairment).
Radiotherapy	In cases of inoperability or incomplete resection of the tumor, irradiation of the tumor area may be considered. If PDS was excised without a safety margin, adjuvant irradiation in order to reduce the rate of locoregional recurrence may be considered.
Medical treatment	Inoperable or metastasized PDS requires individual therapeutic decisions. Treatment with a checkpoint inhibitor appears to be a promising option but requires off-label use.
Follow-up	Physical examination is recommended every six months for AFX and every three months for PDS in the first two years. Thereafter (for at least five years), examinations should be performed every year for AFX and every six months for PDS. This includes palpation and for PDS also ultrasound of the locoregional lymph nodes. Instrumental diagnostics such as cross-sectional imaging are only indicated for suspicious findings, or for primary tumors with special features (such as vascular infiltration) or for recurrent or metastasized tumors.

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Correspondence to

Priv.-Doz. Dr. med. Doris Helbig
Klinik für Dermatologie und Venerologie
Universitätsklinikum Köln
Kerpener Straße 62

50937 Köln
Germany

E-mail: doris.helbig@uk-koeln.de

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