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Elisa Ríos-Viñuela, Carlos Serra-Guillén, Beatriz Llombart, Celia Requena, Eduardo Nagore, Victor Traves, Carlos Guillén, Diego Vázquez, Onofre Sanmartín

In European Journal of Dermatology 2020/5 Vol. 30 , pages 545 to 553
Publisher JLE

ISSN 1167-1122
DOI 10.1684/ejd.2020.3875
Uploaded: 09/23/2024

Investigative report

Eur J Dermatol 2020; 30(5): 545-53

Pleomorphic dermal sarcoma: a retrospective study of 16 cases in a dermato-oncology centre and a review of the literature

Elisa RÍOS-VIÑUELA[1]
Carlos SERRA-GUILLÉN[1]
Beatriz LLOMBART[1]
Celia REQUENA[1]
Eduardo NAGORE[1]
Victor TRAVES[2]
Carlos GUILLÉN[1]
Diego VÁZQUEZ[1]
Onofre SANMARTÍN[1]

[1] Department of Dermatology, Instituto Valenciano de Oncología. Valencia, Spain
[2] Department of Pathology, Instituto Valenciano de Oncología. Valencia, Spain

Reprints: Elisa Ríos-Viñuela
<elisariosvi@hotmail.com>

Article accepted on 19/04/2020

Background: Relatively little is known about the true aggressive potential of pleomorphic dermal sarcoma (PDS) or optimal management strategies. *Objective:* To describe the outcomes of 16 cases of PDS treated at our hospital (14 with modified Mohs micrographic surgery [M-MMS] and two with conventional surgery) and establish an adequate plan for management. *Materials & Methods:* We reviewed 16 PDS cases treated at our hospital between October 2007 and June 2019 and compared our results with the available evidence. *Results:* In total, 69% of cases had recurred after initial conventional surgery, M-MMS led to local disease control in 83% of cases, and 19% of patients developed metastasis. Combining all published PDS cases with ours, we calculated an overall metastasis rate of 12%, and an overall recurrence rate of 35% after conventional surgery and 17% after M-MMS. *Conclusion:* PDS is more aggressive than previously estimated, with an overall metastatic rate of 12%. Despite high recurrence rates with previous conventional surgery (69%), M-MMS achieved a good rate of local disease control (83%). Given the potential aggressivity of PDS and the importance of clear surgical margins, M-MMS appears to be more adequate than conventional excision. Staging studies and close monitoring are warranted in PDS patients, for which we propose a management algorithm.

Key words: pleomorphic dermal sarcoma, micrographic Mohs surgery, Mohs surgery, atypical fibroxanthoma, wide local excision, sarcoma

The term *atypical fibroxanthoma* (AFX) was first introduced by Helwig [1, 2] in 1961 to describe a dermal neoplasm characterized by a high proliferative rate and marked cellular pleomorphism, however, presenting with a usually non-aggressive clinical behaviour [3-10]. Its definition and relationship with malignant fibrous histiocytoma (MFH) have been the subject of intense debate in the literature, and the nomenclature regarding these entities has suffered multiple confounding changes through the years [8, 11, 12]. Owing to advances in immunohistochemistry and molecular biology, many of the mesenchymal neoplasms of uncertain origin, previously included in the spectrum of MFH, have been reclassified as other tumours (*e.g.*, angiosarcoma, cutaneous squamous cell carcinoma [cSCC], and even melanoma) or recategorized as independent entities, and the use of this term has decreased progressively [6, 13-19]. With the 2013 update of the World Health Organization Classification of Soft Tissue Tumours, the term *undifferentiated pleomorphic sarcoma* was proposed to describe mesenchymal tumours with an unclear line of cellular differentiation [2, 6, 13-15, 19]. Concurrently, in 2012, the term *pleomorphic dermal sarcoma* (PDS) started being used to describe dermal-based tumours without a clear line of differentiation that had overlapping histological features with AFX, but at least one of the following features: perivascular invasion, perineural invasion, necrosis, and evident subcutis invasion [1, 2, 6, 15]. The presence of one or more of these features is diagnostic of PDS, which unlike AFX does not exhibit a benign or indolent behaviour [2-4, 6, 9, 20-22]. Currently, PDS and AFX are considered by most to be part of the same tumour spectrum, with PDS being the deeper, more aggressive variant [2, 6, 9, 10, 15, 23, 24]. Both entities affect chronically sun-exposed skin in elderly patients, and are characterized histologically by a mixed proliferation of spindle and epithelioid pleomorphic cells, atypical multinucleated cells, and abundant mitotic figures [1, 2, 4, 6, 9, 15, 20, 25]. Because of the low incidence of PDS and historical terminological confusion, there are very few studies concerning this tumour's true aggressive potential or optimal management strategies [2, 6, 15, 20]. The metastasis rate of PDS has traditionally been estimated at around 5% [2, 7], but more recent data suggest that it may be as high as 20% [1, 2, 26]. Although recent studies have shown lower recurrence rates for AFX treated with Mohs micrographic surgery (MMS) compared with wide local excision [6, 27, 28], there are currently no standardized management guidelines for PDS [1, 2, 6, 15, 20, 26]. To help define optimal treatment and prognosis for PDS, we conducted a retrospective observational study of PDS cases treated at our hospital, and carried out a review of the literature published since the introduction of the new classification system in 2012.

doi:10.1684/ejd.2020.3875

To cite this article: Ríos-Viñuela E, Serra-Guillén C, Llombart B, Requena C, Nagore E, Traves V, Guillén C, Vázquez D, Sanmartín O. Pleomorphic dermal sarcoma: a retrospective study of 16 cases in a dermato-oncology centre and a review of the literature. *Eur J Dermatol* 2020; 30(5): 545-53 doi:10.1684/ejd.2020.3875

Methods

We conducted a retrospective observational study of 16 PDS cases treated at the Instituto Valenciano de Oncología, in Valencia, Spain between October 2007 and June 2019. All the data were retrieved from the patients' medical records and from the Pathology Department's database. Eleven of these 16 cases were referred to us from other institutions, as we are a referral centre in dermato-oncology. Informed consent was obtained from patients following the procedures established by the ethics committee at our hospital. PDS diagnosis was established based on: (1) a dermal mesenchymal neoplasm with pleomorphic spindle and/or epithelioid cells and an unidentified line of differentiation based on the immunohistochemical study (absence of cytokeratin, caldesmon, protein S100, and CD34 expression); and (2) the presence of at least one of the following features: evident subcutis infiltration, perivascular invasion, perineural invasion, and/or necrosis. Additional immunohistochemical studies included smooth muscle actin (SMA), vimentin, CD10, CD68 and CD99. The depth of invasion was also studied. A histological review of all the cases was performed by two experienced dermatopathologists (Dr Traves, Dr Sanmartin) and three dermatologists (Dr Rios-Viñuela, Dr Serra-Guillén, Dr Llombart), who re-examined all available haematoxylin-eosin-stained sections and immunohistochemistical data. The clinical factors studied, and management and follow-up parameters, are presented in *tables 1 and 2*, respectively. Conventional surgery was defined as wide local excision with 2-cm margins. Modified MMS was performed using formalin-fixed, paraffin-embedded, horizontal sections following the standardized procedure used at our hospital [29-31]. The cyclic process of excision, mapping, and microscopic examination was repeated until there was no microscopic evidence of tumour or until unresectable structures were reached. We reviewed the available literature regarding PDS published since 2012 (included), and compared the results of the three main series published so far with ours. Based on our experience and on the available evidence, we developed a management algorithm for PDS/FXA.

Results

Clinical and histological data

Clinical data are presented in *table 1* and *figure 1*. Twelve of the 16 PDS cases (75%) had initially been diagnosed as AFX. Eleven cases were referred to us, 10 of which had recurred following initial wide local excision. When first evaluated by us, six cases were primary and 10 were recurrent tumours. Overall, 11 cases (69%) recurred after wide local excision, seven of which (64%) recurred twice or more times. The main factor associated with recurrence was initial resection with positive surgical margins (7/11 cases; 64%). First recurrence occurred at a median of six months (range: 1-11 months), and second recurrence occurred at a median of five months after the previous recurrence (range: 1-7 months). Progression to locally advanced disease or lymph node or visceral metastasis was observed in nine cases (56%). Metastasis occurred in three cases (19%; two visceral metastases and one nodal metastasis).

All cases were consistent with an unidentified line of differentiation. All cases were vimentin and CD10 positive, eight cases were positive for CD68, and three cases were positive for CD99. The median depth of invasion (Breslow) was 7.3 mm (3.7 mm to 14 mm). Histological features of some PDS cases are presented in *figure 2*.

Management and follow-up

Management and follow-up data are summarized in *table 2* and *figure 3* An imaging study (computed tomography [CT] or magnetic resonance imaging [MRI]) was used for preoperative surgical planning in patients with locally advanced disease (which we considered as deeply infiltrating and/or very large tumours, although there is no consensus for the definition of locally advanced disease in PDS). Two cases were treated with wide local excision, both of which were small primary tumours that were diagnosed in our department; Patient 1 underwent further lateral margin enlargement because of minimal lateral margin positivity in the first excision. All remaining cases (14 patients) were treated with modified MMS. Negative surgical margins were obtained (requiring between one and three stages) in 12 cases (86%), two of which had disease recurrence during follow-up. Thus, the local control rate (maintained during follow-up) was 83% (10/12). Two patients with locally advanced disease, considered to be particularly high-risk (invasion of the periosteum), underwent local skull drilling and received adjuvant radiotherapy; one of whom had a recurrence. The two patients with visceral metastasis underwent modified MMS to achieve local disease control, however, metastatic disease was detected in the staging study performed immediately afterwards (no staging studies were performed prior to surgery). The patient with lymph node metastasis already had nodal involvement when referred to our hospital. The two patients with visceral metastasis were treated with chemotherapy (taxanes and gemcitabine in Patient 7 and pazopanib in Patient 8). Both died due to disease progression.

Median follow-up was 18 months (range: 2-99 months). Patients 5 and 11 were lost to follow-up. Follow-up was limited in many cases due to the patients' advanced age and comorbidities and because some patients returned to the referring hospital for follow-up.

A management algorithm for staging studies and close monitoring in PDS patients is presented in *figure 4*.

Discussion

The true aggressive potential and prognosis of PDS remain unclear because of the low incidence of this tumour, the historical confusion surrounding its nomenclature, and the paucity of cases published since the unification of diagnostic criteria [1-6, 9, 14, 15, 20, 26, 27, 32]. In contrast to the classic estimate of 5% [2, 7], recent studies reported metastatic rates ranging between 9% and 20% [1, 2, 26]. The metastases were located in the skin, regional lymph nodes, and the lungs. In our series, two patients developed visceral metastasis and one developed lymph node metastasis, and at least two of these patients died of disease progression. Although our hospital is a referral centre for dermato-oncology which may have created a bias for

Table 1. Clinical characteristics.

Case	Hospital of origin	*Tumour* type*	Age	Sex	*Non-melanoma* skin cancer	Location	Size (mm)	Time since onset (months)	Initial diagnosis	First excision with negative margins	Number of recur-rences	Locally advanced disease	Metastasis	Died from disease
1	Our hospital	P	70	Male	Yes	Scalp	13	2	AFX	Yes	1	No	No	No
2	Other	R	79	Male	No	Scalp	60	14	AFX	No	≥ 2	Cranial vault	No	No
3	Other	R	80	Male	Yes	Forehead	20	4	AFX	No	≥ 2	Periosteum	No	No
4	Other	P	85	Male	No	Nose	20	6	PDS	No	No*	No	No	No
5	Other	R	84	Male	No	Ear	39	6	AFX	Yes	≥ 2	Cartilage	No	No
6	Other	R	80	Male	Yes	Scalp	26	NA	AFX	No	≥ 2	Cranial vault	No	No
7	Other	R	70	Male	No	Scalp	?	12	AFX	No	≥ 2	No	Lung	Yes
8	Other	R	84	Male	Yes	Scalp	32	6	AFX	Yes	≥ 2	Temporal muscle	Lung and brain	Yes
9	Other	R	71	Female	Yes	Nose	30	3	AFX	No	1	No		No
10	Our hospital	P	93	Male	Yes	Scalp	39	6	PDS	No	≥ 2	Cranial vault	No	No
11	Other	R	71	Male	No	Ear	13	6	AFX	No	1	Ear pin Parotid gland	Lymph nodes (regional)	NA
12	Other	R	85	Female	Yes	Temple	19.5	6	AFX	Yes	≥ 2	No	No	No
13	Our hospital	P	89	Male	Yes	Scalp	13	NA	AFX	Yes	No	No	No	No
14	Other	R	75	Male	Yes	Scalp	16.9	NA	AFX	No	1	No	No	No
15	Our hospital	P	85	Male	No	Scalp	35	3	PDS	Yes	No	Epicranial aponeuro-sis	No	No
16	Our hospital	P	86	Male	Yes	Scalp	15	NA	PDS	Yes	No	No	No	No

* *Tumour type refers to primary tumour (P) or recurrences(R); we consider recurrence as a tumour that had already recurred at least once before being referred to our centre. Primary tumours are underlined.*
** *Not considered as recurrence, as the patient was referred for Mohs micrographic surgery after incomplete initial excision.*

Table 2. Management and follow-up.

Patient	*Tumour* type (primary or recurrent)	Initial treatment	Subsequent treatments	Number of modified MMS stages	Negative margins	Adjuvant therapy	Subsequent outcomes	Follow-up (months)
1	Primary	Conventional surgery*	Margin enlargement	-	Yes	-	No recurrences	99
2	Recurrent	Conventional surgery	Modified MMS	1	No	Cranial bone drilling + adjuvant RT; pazopanib was proposed but not started (patient died)	Lithic lesions in cranial bone+ possible meningeal invasion; Died due to comorbidities	21
3	Recurrent	Conventional surgery	Modified MMS	3	Yes *(doubtful)*	Recurrence: New MMS stage + cranial bone drilling + adjuvant RT	No further recurrences	54
4	Primary	Conventional surgery	Modified MMS	1	Yes	-	No further recurrences	12
5	Recurrent	Conventional surgery	Modified MMS	-	Yes	-	-	2 (lost)
6	Recurrent	Conventional surgery	Modified MMS	3	Yes	Recurrence: New MMS stage	No recurrences Died due to comorbidities	53
7	Recurrent	Conventional surgery	Modified MMS	1	Yes	Adriamycin taxanes + gemcitabine	Lung metastasis Died from disease	16
8	Recurrent	Conventional surgery	Modified MMS	1	Yes	Pazopanib Palliative whole-cranial RT	Lung + brain metastasis Died from disease	17
9	Recurrent	Conventional surgery	Modified MMS	1	Yes	-	No recurrences	24
10	Primary	Modified MMS	-	1	No	Palliative therapy	Died due to comorbidities	14
11	Recurrent	Conventional surgery	Modified MMS	1	Yes	-	Lymph node metastasis (before MMS)	2 (lost)
12	Recurrent	Conventional surgery	Modified MMS	2	Yes	-	No recurrences	3
13	Primary	Conventional surgery*	-	-	Yes	-	No recurrences	3
14	Recurrent	Conventional surgery	Modified MMS	1	Yes	-	No recurrences	70
15	Primary	Modified MMS	-	2	Yes	-	No recurrences	2
16	Primary	Modified MMS	-	1	Yes	-	No recurrences	22

MMS: Mohs micrographic surgery; RT: radiotherapy. * *Cases 1 and 13 were treated with conventional surgery only and did not receive treatment with modified MMS.* ** *Number of recurrences is shown in brackets in cases with more than one recurrence.* *** *Not considered recurrence as the patient was referred for Mohs micrographic surgery after incomplete initial excision.*

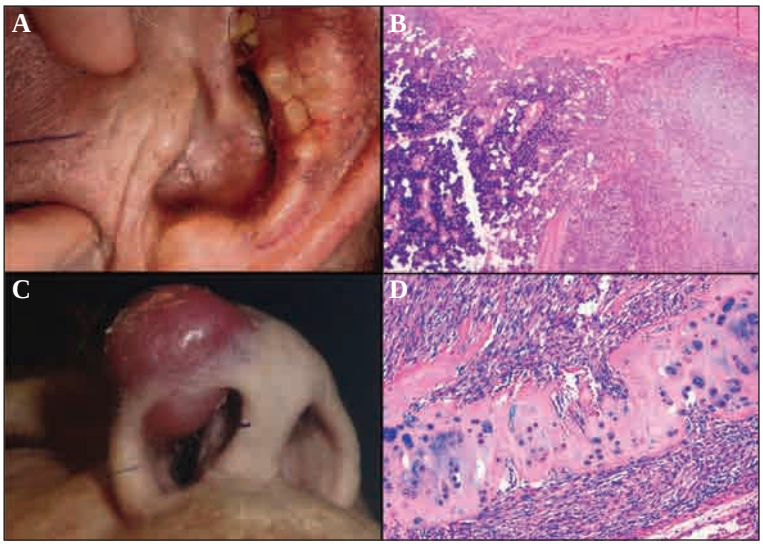

Figure 1. Clinicopathologic correlation in two PDS cases: **A**, **B**) Case 11: metastatic nodal involvement from PDS, originally from the left ear; the histological image shows tumoral invasion of the neighbouring parotid gland. **C**, **D**) Case 9: a nodular erythematous tumour with evident clinical invasion of the nasal cartilage; the histological image shows obvious cartilage invasion by neoplastic proliferation of spindle cells.

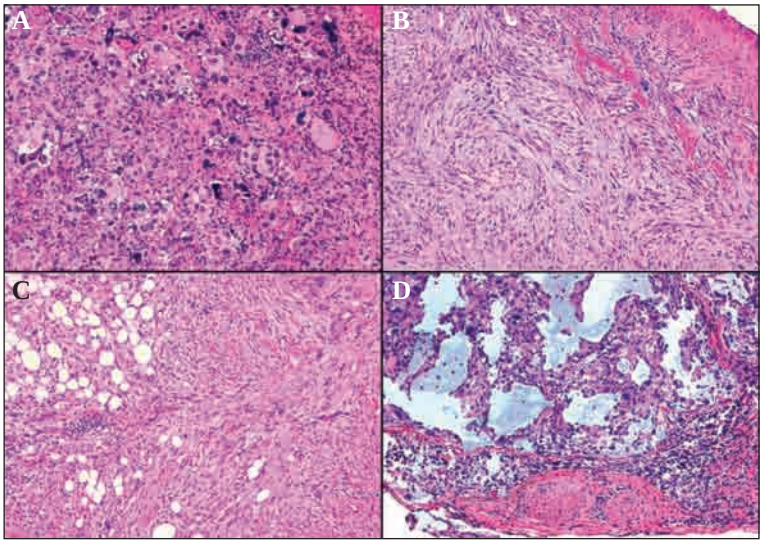

Figure 2. Histological features of some of the cases included in our series. **A**) Case 6: highly pleomorphic, epithelioid cells with marked nuclear atypia and some pyknotic nuclei; some of these cells display xanthomatous changes. **B**) Case 15: dense dermal proliferation of pleomorphic spindle cells; the overlying epidermis is ulcerated. **C**) Case 15: marked subcutis invasion by pleomorphic spindle cells. **D**) Case 8: discohesive, pleomorphic cells appear to be floating in a mucinous stroma, with perineural involvement in the lower part of the image.

higher-risk PDS cases, our 19% metastatic rate falls within the range established by the other series [1, 2, 26]. Combining their results with ours, we calculated an overall metastatic rate of 14.5%, which is significantly higher than the classic estimate [2, 7].

It is essential to distinguish between AFX and PDS as these differ in both clinical behaviour and aggressive potential [1, 2, 6, 9, 15, 20]. Based on strict diagnostic criteria, the behaviour of AFX is eminently benign [1, 2, 6, 9, 15, 20]. In fact, in a literature review guided by these criteria, we found just one convincing case [33] of metastatic AFX [1, 6, 11, 15, 16, 21, 34-36]. Precise evaluation of diagnostic criteria requires a sufficiently large and deep sample (ideally, an *in toto* specimen), and superficial biopsy is thus inadequate [1, 2, 4, 6, 15, 20]. Diagnostic errors are relatively common and account for why tumours that would now fall into the category of PDS were previously described as locally aggressive or metastatic AFX [1, 2, 6, 15, 17]. Twelve of the 16 tumours in our series were initially diagnosed as AFX, but were later recategorized as PDS because they showed some of the aggressive histological features described earlier and/or followed an aggressive clinical course. These findings highlight the critical importance of a precise, systematic histological examination,

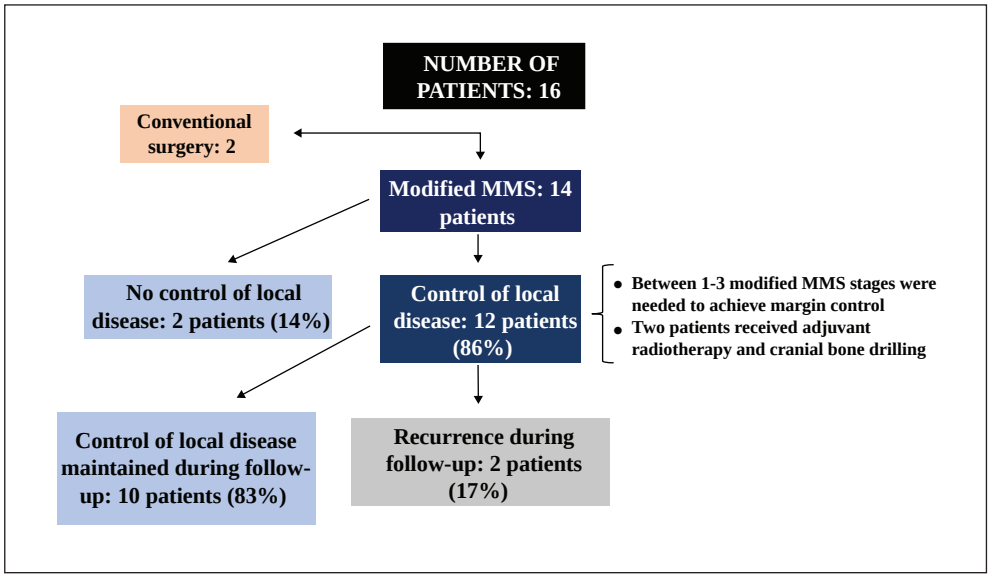

Figure 3. Outcome flow chart highlighting treatments and outcomes of the patients included in our series.

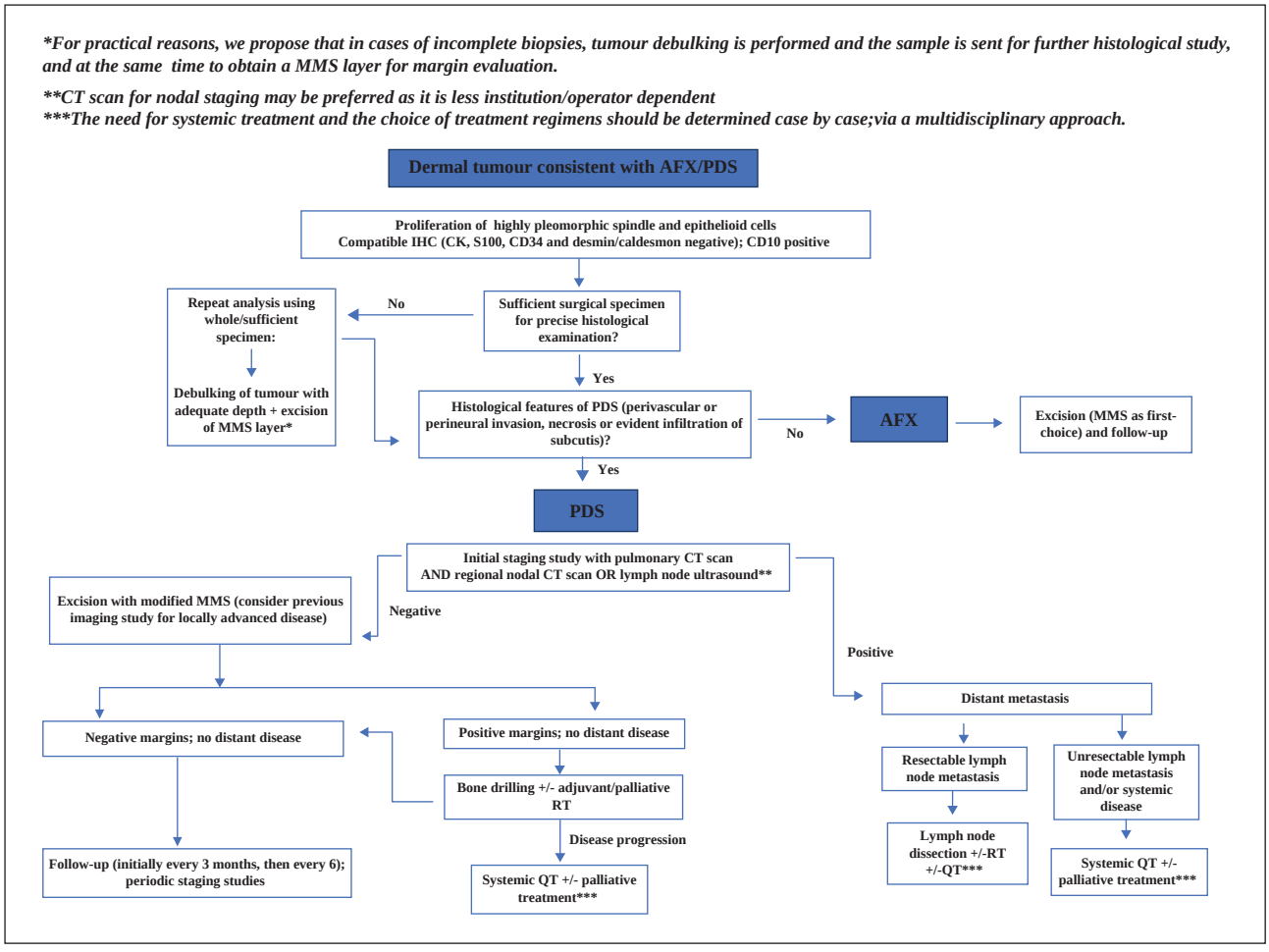

Figure 4. Algorithm for diagnosing/treating PDS.

Table 3. Literature review and combined data.

Series or Case	Number of patients	Patient characteristics	Treatment	Subsequent outcome	Follow-up (months)
Persa et al. [*26*]	92	100% primary	Conventional surgery	Recurrence 28% (26 cases) Metastasis 9% (8 cases)	18 (median)
Miller et al. [*1*]	32	100% primary	Conventional surgery	Recurrence: 28% (8 cases) Metastasis: 20% (3 cases)	24 (median)
Tardío et al. [*2*]	18	100% primary	Conventional surgery	Recurrence: 20% (3 cases) Metastasis: 20% (3 cases)	33 (median)
Kravvas et al. [*42*]	1	100% primary	Conventional surgery + RT	Local recurrence Lung metastasis Died	11
Anderson et al. [*19*]	1	100% multifocal presentation	Liposomal doxorubicin	Died	2
Mesbah Ardakani et al. [*43*]	1	100% primary	Conventional surgery + RT	Recurrence	3
Rupal Sharma et al. [*44*]	1	100% primary	Conventional surgery	NA	NA
Crimini et al. [*45*]	1	100% primary	1st: conventional surgery Recurrence: electrochemotherapy	1st: recurrence 2nd: no recurrence	3
Klebanov et al. [*46*]	1	100% primary	Conventional surgery	Recurrence	1
Kim et al. [*47*]	1	100% primary	MMS	Recurrence	24
Nergard et al. [*36*]	1	100% primary	1st: MMS 2nd: MMS (for local recurrence) 3rd: RT of cranial vertex	Local recurrence → single cutaneous metastasis → several cutaneous metastases on vertex	20
Muller et al. [*48*]	1	100% primary	1st: conventional surgery Recurrence: excision of metastasis + adjuvant RT	Local recurrence x3 Lung Metastasis	20
Our series	16	25% primary 75% recurred	Modified MMS:14 Conventional surgery only: 2	Modified MMS 83% → local control; 14% recurrences Conventional surgery → Overall 69% recurrences (including recurrences after conventional surgery prior to MMS) 19% metastasis (3 cases)	16 (median)
TOTAL	167	93% primary tumours 7% recurred tumours	Conventional surgery (± other adjuvant therapies): 90% Modified MMS: 8% MMS: 1% Other treatments: 1%	Recurrence rate after modified MMS: 17% Overall recurrence rate after conventional surgery *: 35% Overall metastasis rate: 12%	15**

including a broad immunohistochemical study to rule out other neoplasms [1, 2, 4, 6, 15, 16, 20, 37].

Surgical excision is the treatment of choice for PDS [1-3, 6, 15, 20, 37]. Positive surgical margins are the main risk factor for local recurrence, hence the importance of complete excision [1, 2, 6, 15, 20]. Persa *et al*. recently identified surgical margins < 2 cm as a main risk factor for relapse [26]. Tardío *et al.* [2] and Miller *at al*. [1] found that positive margins were associated with an increased risk of metastasis, highlighting even further the importance of clear surgical margins. While recurrence rates reported by recent studies (in which all included cases were treated with conventional surgery) ranged between 20% and 28% [1, 2, 26], 69% of the cases in our series recurred at least once after conventional surgery (64% of which had positive margins). Several recent studies comparing MMS and wide local excision for AFX demonstrated lower recurrence rates and better preservation of healthy tissue with MMS [1, 2, 27, 28]. However, no studies to date have examined the performance of MMS for PDS [6, 15, 20]. In our series, modified MMS achieved tumour-free margins in 86% of cases with a local control rate of 83%, maintained during follow-up. The rate of local disease control achieved with micrographic MMS is remarkable, especially taking into account the high recurrence rate after conventional surgery observed in our series. In this study, conventional surgery and modified MMS were not directly compared, however, based on our findings and on the little available evidence, modified MMS appears to be more adequate for the treatment of PDS, and thus we consider it the treatment of choice for this tumour. Undoubtedly, further investigation will be needed to further support this conclusion.

Adjuvant radiotherapy and/or chemotherapy is warranted for patients with advanced or metastatic disease, although clear evidence on the effectiveness of these treatments is lacking [14, 15, 20]. Traditionally, radiotherapy has been used in a strictly adjuvant or palliative role to treat locally advanced/unresectable disease [6, 15, 20]. In our series, two patients with locally advanced PDS of the scalp (periosteum invasion) underwent burr hole craniostomy with adjuvant radiotherapy and one of these experienced recurrence during follow-up. The two patients with visceral metastasis were treated with systemic chemotherapy, and both died from disease progression. Recent data suggest that PDS may be a candidate disease for immunotherapy [25, 38, 39].

There are no standardized recommendations for staging and follow-up for PDS [1, 2, 6, 14, 15, 20]. Two recent review papers proposed equating the spectrum of AFX/PDS to that of cSCC/high-risk SCC, using an analogous management and follow-up plan [4, 11]. A full-body examination should be performed in all patients diagnosed with PDS, as these patients often have other skin tumours [6, 15]. Bearing in mind the metastatic risk discussed above, we consider that a staging study is warranted, at least initially and most probably periodically during the first years of follow-up. This would be particularly important in patients who have experienced multiple recurrences or with locally advanced disease [6, 20]. Staging recommendations for soft tissue sarcomas vary between different guidelines, but all stress the need for a chest X-ray or CT scan (which demonstrates better sensitivity) to rule out metastatic lung disease [6, 15, 20, 26, 40, 41]. Lymph node metastasis should be ruled out based on a regional CT scan or MRI, or alternatively, ultrasonography of regional lymph node basins [26, 41]. Drawing on guideline recommendations for high-risk cSCC, we suggest initial follow-up every three months for the first one or two years and thereafter every six months for at least five years (*figure 1*) [6, 15].

Finally, *table 3* outlines the clinical characteristics, treatments, and outcomes for all PDS cases (both series and case reports) published since the 2012 nomenclature update. Unlike our study, all other cases were primary tumours. The vast majority were treated with wide local excision and overall recurrence rates during follow-up were relatively high; up to 35% for tumours treated with conventional surgery recurred at least once during follow-up. To our knowledge, only two cases of PDS treated with conventional MMS have been published to date, both of which recurred during follow-up, and we believe more studies are needed to assess its true efficacy as a treatment for this tumour. The overall metastatic rate (including our series) is around 12%.

Conclusions

Although the true aggressive potential of PDS is unknown, current evidence suggests that recurrence and metastatic rates are higher than previously estimated, highlighting the importance of clear surgical margins. In our study, modified MMS achieved a high rate of local disease control despite the high recurrence rate after conventional surgery. Based on our experience and on the little available evidence, we consider modified MMS to be more adequate than conventional surgery for PDS management. Considering the aggressive potential of PDS and guideline recommendations for high-risk cSCC, we recommend performing a full staging study, particularly during the first years of follow-up. More studies are needed to optimize guidelines for PDS management and follow-up. ■

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