

REVIEW ARTICLE

Dermatofibrosarcoma protuberans: a rare entity and review of the literature

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Summary

Dermatofibrosarcoma protuberans (DFSP) is an uncommon malignant mesenchymal tumor. The incidence of DFSP is 0.1% of all cancers and less than 2% of all soft tissue sarcomas (STS). It can appear at any age, most commonly in individuals aged between 20 and 50 years. The usual location of DFSP is the trunk and it is limited to the dermis. Wide radical excision is the preferred surgical method for therapy of DFSP without distant metastasis. The

probability of regional or distant metastases is less than 5%. Patients with positive or close surgical margins have an elevated risk of local recurrence after resection. Adjuvant radiotherapy administered either before or after the surgical treatment reduces the risk of local recurrence.

Key words: dermatofibrosarcoma protuberans, positive margins, radiotherapy, soft tissue tumor

Introduction

DFSP is a rare monoclonal cutaneous soft tissue sarcoma that was first described by Taylor in 1890. It accounts for approximately 1.8% of all STS [1]. DFSP is characterized by slow infiltrative growth, but it is locally aggressive, having a high potential for local recurrence if not treated properly. However, DFSP generally exhibits low metastatic potential. Distant metastases are extremely rare ($\leq 5\%$) and generally occur as a late sequel after local recurrences [1-3]. Limited experience with conventional chemotherapy suggests that it has no significant benefits in the treatment of locally advanced or metastatic DFSP. Most of these lesions are fixed to the overlying skin but not to deeper subcutaneous structures [1,4,5]. Fixation to more deeply seated structures is often observed only in advanced or recurrent cases of DFSP [3].

Molecular pathogenesis

Research suggests that many cases of DFSP (more than 90%) arise from the rearrangement of chromosomes 17 and 22 and they are characterized by a supernumerary ring chromosome composed of hybrid material derived from t(17;22) [4,6-8]. The translocation that occurs has as a result the fusion of the collagen Type Ia1 gene (COL1A1) with the platelet derived growth factor (PDGF) β -chain gene (PDGFB). This rearrangement leads to continuous activation of the PDGF receptor β protein tyrosine kinase, via autocrine and paracrine production of its functional ligand [3]. The COL1A1 - PDGF fusion product can be detected by fluorescence *in situ* hybridization (FISH) or multiplex reverse-transcriptase polymerase chain reaction (RT-PCR), a fact that can be useful for diagnostic reasons. However, there is a group of cases of DFSPs that this fusion product cannot be detected (<8%), suggesting that there are other genes that

may be involved in this translocation. Histologically, PDGF is composed of benign – appearing spindle cells arranged in an irregularly whorled or storiform pattern [9]. A history of trauma (10-20%) in the region affected is reported as a possible etiological factor of DFSP. However, there are cases that have been associated with surgical scars, trauma scars, burns, vaccination scars or even radiodermatitis. Also, there is a reported case of a DFSP arising in a decorative tattoo region [5,10]. Six other cases are reported arising in a bacillus Calmette-Guerin vaccination scar [11]. However, there are uncommon variants of DFSP including the Beduar tumor, which is characterized by the presence of melanin-containing dendritic cells and myxoid DFSP. Furthermore, approximately 10-15% of all DFSP contain a fibrosarcomatous component. The sarcomatous component has 2-16 mitoses per 10 high-power fields (HPF) compared to 0-3 mitoses per 10 HPF in the DFSP component [3]. This is the reason that there is a new therapeutic approach which is based on targeted inhibition of the PDGFR protein tyrosine-kinase [12].

Epidemiology

Malignant soft tissue tumors are relatively rare and account for only 0.8-1% of all cancers and 1-1.8% of all STS [11]. However, examining only cutaneous tumors, DFSP is the most common sarcoma of cutaneous origin. It has been recently reported that there is an increase in the incidence of DFSP, as an improvement of methods capable to recognize the distinct features of DFSP [11]. According to recent studies DFSP can be regarded as an uncommon but not rare STS whose increased frequency of detection over the last 30 years reflects the increasing awareness of its clinical manifestations. The majority of the patients are in the mid-adult life, or at least this is the mean age that it is diagnosed, since DFSP is characterized by its slow growth [4,10,11,13]. It has to be noticed that there are a few reported cases of DFSP in children, while there are 5 cases with DFSP being present since birth [11,13].

DFSP develops more frequently in males than in females.

Clinical presentation

The most common location of DFSP is on the trunk. Fifty percent of all reported cases are located on the trunk, mainly the chest and shoulder. Other less usual locations of DFSP are the limbs (30-40%) and head and neck (10-15%). It has to be mentioned that treatment is less effective in cases

of DFSP on the head and neck and the possibility of invasion is higher there [4,14,15]. In the literature, there are 6 cases that have been reported involving the hands or the feet [11].

DFSP is a slow growing tumor and, as a consequence, patients ask for a medical opinion at a late stage. The clinical appearance of the tumor depends on the time since onset. It usually progresses slowly over a long period of time, while afterwards it enters in a rapid growth phase, with the development of multiple nodules. DFSP arises as pink or violet – red plaques, while the surrounding skin may be telangiectatic [3]. During the initial stages of DFSP the main protruding characteristics are not visible. Murphey et al. [6] and Moureau-Zabotto et al. [13] studied the clinical characteristics at early stage and they classified 3 different forms of non-protruding DFSP: (i) morphea-like, characterized by the formation of a white or brown indurated plaque with the appearance of a scar, morphea, morpheaform basal cell carcinoma, or dermatofibroma plaque; (ii) atrophoderma-like, characterized by a soft depressed white or brown plaque that appears similar to atrophoderma or anetoderma; and (iii) angioma-like, the least common form, made up of indurated or soft, red or violaceous plaques that have a clinical appearance similar to vascular malformations or such as morphea-like plaques, and congenital cases, such as atrophoderma-like, are more common, particularly when the lesions are located on the trunk [3,9].

The initial size of the lesion at the early stage is 2-5 cm. However, this remains undiagnosed, since the patient doesn't ask for medical advice, so the lesion may reach even 25cm in diameter or larger. The tumor is initially firmly fixed to the overlying skin but not to underlying deeper structures, except for those lesions involving the scalp, where periosteal attachment occurs very early [11]. After a long period of slow growth, the tumor enters a rapid growth phase and becomes fixed to deep subcutaneous structures.

Diagnosis

In most of the cases, DFSPs are typically small and superficial. Diagnosis may be suspected on the basis of the tumor's clinical appearance, while physical examination may assess the extension of the tumor. Lymphatic or haematogeneous dissemination is rare, however lymph nodes are assessed by palpation [3]. Magnetic resonance imaging (MRI) is very useful for the estimation of the tumor invasion, mainly in cases of large tumors or large recurrent lesions. Furthermore, MRI can pro-

vide valid information about the accurate position of the tumor, while is an effective method for the differential diagnosis in cases of tumors that occur in an atypical site [16]. Conventional T1-weighted images show hypointense lesions compared to subcutaneous fat [3]. However, it can be hard to separate DFSP from fat on conventional T2-weighted images without fat saturation. Finally, enhancement can be variable and depends on the levels of necrosis or hemorrhage [16].

Computed tomography (CT) is not indicated for DFSP diagnosis. However, it is very useful in cases where underlying bone involvement is suspected or in case of pulmonary metastases [3]. Finally, in cases of very large DFSPs CT is indicated as the imaging of the tumor is more distinct [3,4].

In the plaque type of DFSP, slender tumor cells with large, spindle-shaped nuclei are embedded fairly uniformly in the collagen stroma, parallel to the skin surface. Mitotic figures are sparse. The more characteristic findings are seen in the nodular type. These findings include high cellularity and irregular, short, intersecting bands of tumor cells forming a storiform pattern. Also typical are cells radiating from a central hub of fibrous tissue forming a cartwheel pattern. The degree of cellular atypia is higher in nodular lesions than in plaque lesions. Occasionally, DFSP may show focal fibrosarcomatous changes with a characteristic herringbone pattern. Cellular atypia is then even more prominent with hyperchromatic nuclei and more mitotic figures [17,18]. The most important characteristic of DFSP is the fact that it can invade surrounding tissues even far from the central focus of the tumor [3,4]. DFSP tumor cells take over the dermis and subcutaneous adipose tissue and then approach the fascia plane. The tumor nodule manifests high cellularity. Under histopathologic examination, these DFSP cells are spindle-shaped. They tend to grow in a storiform pattern in the central portion of the tumor. They may also grow in a diffuse infiltrative pattern at the periphery, forming a honeycomb pattern. Often, no defined border can be recognized between the tumor and normal tissue. DFSP demonstrates strong CD34 staining with immunohistochemistry. In the pigmented variant of DFSP, also known as Bednar tumor, the melanin-containing dendritic cells are scattered between the neoplastic spindle-shaped cells [19]. In the juvenile form (giant cell fibroblastoma), cleftlike pseudovascular spaces are lined by multinucleated cells. The intervening tumor may have loose hypocellular areas and areas that resemble mature DFSP.

Immunohistochemistry studies have shown

moderate-to-strong staining of human progenitor cell antigen CD34 in tumor cells. CD34 is a useful marker that allows differentiation of DFSP cells from normal stroma cells and dermatofibroma. In dermatofibroma, tumor cells are positive for factor XIIIa and are rarely positive for CD34. Additionally, immunostaining with CD34 as a marker is helpful in identifying tumor cells at the surgical margins, particularly when treating recurrent DFSP in which tumor cell fascicles are often interspersed with the scar tissue [20].

Differential diagnosis

Differential diagnosis includes dermatofibroma, epidermal inclusion cyst, keloid and hypertrophic scar, melanoma, morphea, lymphoma and fibrosarcoma [21]. Their differences concern the structure of the tumors, their cells, the rate of metastases and recurrence after conservative therapy [11] (Tables 1,2). The distinction between dermatofibroma, particularly the cellular variant, and DFSP in excisional biopsies is usually straightforward. However, a separation between the two may be sometimes challenging, especially in superficial biopsies. Although factor XIIIa and CD34 immunostains are useful in differentiating dermatofibroma and DFSP in most instances, focal CD34 positivity may be seen in cellular fibrous histiocytoma. Some cases reveal overlapping immunostain results. D2-40 identifies a 40-kDa O-linked sialoglycoprotein present in a variety of tissues including testicular germ cell tumors as well as lymphatic endothelium. To date, there

Table 1. Immunohistochemical differences between dermatofibrosarcoma protuberans (DFSP) and dermatofibroma

	DFSP	Dermatofibroma
CD34	+	+/-
CD44	-	+
XIIIa	-	+
p75	+ (95%)	-

Table 2. Differential diagnosis of dermatofibrosarcoma protuberans (DFSP) and dermatofibroma

DFSP	Dermatofibroma
Grotesque nodular configuration	Slightly elevated nodule with discolored surface
Infiltration of subcutaneous tissue	No infiltration of subcutaneous tissue
Recurrence rate >5%	Recurrence rate <5%
Dendritic cells containing melanin	Spindle cells with xanthomatous and hemosiderin-laden histiocytes and inflammatory cells

are controversies and uncertainties regarding the histiogenesis of dermatofibromas and DFSP. For dermatofibroma, various cells of origin, including fibroblast, histiocyte, and endothelial cells, have been hypothesized. Some authors suggested myofibroblastic origin for cellular fibrous histiocytoma, given its reactivity for α 1-smooth muscle actin. On the basis of the characteristic immunoreactivity for factor XIIIa in dermatofibroma, several groups postulated an origin from dermal dendrocytes [20,22-24]. Unlike dermatofibroma, earlier immunohistochemical and ultrastructural studies suggested that DFSP may be originated from fibroblasts. A more recent report indicated that DFSP is probably a neuromesenchymal neoplasm based on the observations in Bednar tumors [25].

Staging

DFSPs are staged in accordance with the American Musculoskeletal Tumor Society (MSTS) staging system, which takes into account tumor grade and compartmentalization [26].

Stage IA: Low grade DFSP with no extension beyond the subcutaneous compartment which can be managed by a wide excision.

Stage IB: Low grade DFSP with extension outside of an anatomic compartment, with involvement of underlying fascia or muscle.

Treatment

DFSP is a locally aggressive tumor characterized by low rate of metastasis and high capacity for local invasion. Consequently, the treatment of choice is resection with wide margins. In the early 1990s the gold standard of treatment for DFSP was surgical excision, with 3-5cm margins of healthy skin, while the underlying subcutaneous tissue, including fascia, was removed *en block* [27].

However, the studies of that period showed the mean rate of recurrence with this technique was 43% (range: 26 - 60%), especially for tumors located on the head and neck [27]. In the late 1990s, an excision with larger margins was used [18,19] leading to amelioration of the recurrence was rate (23%) [6,27], although the disease free interval was not what it was expected. The idea of using even more wide margins of excision led to unnecessary removal of healthy and potentially useful tissue, so it was abandoned. This approach was reinforced by the fact that DFSP is not characterized by concentric growth, so a traditional vertical section might not remove a potentially asymmetric part of the tumor. In the 1970s, Mohs applied a micrographic surgical technique, which was used

for DFSP a few years later [28-31]. Treatment for DFSP was improved by practicing the Mohs Micrographic Surgery (MMS). Several retrospective studies demonstrated considerably better recurrence rates (0 - 0.6%) [27].

Excision by means of MMS [6,32,33], with continuous histological margin control, is an attractive surgical option because it is potentially tissue-sparing. MMS superiority is based on the fact that the margins are performed intraoperatively, so that the amount of the tissue excised can be minimised, especially in invisible areas [34]. Furthermore, MMS is an effective surgical tool for body regions where wide excision is not feasible or desirable (hand or toe). DuBay et al. [35] were one of the first groups that used this technique and reported a 0% recurrence rate in 42 patients after a 4-year follow-up.

However, MMS may be utilized only in local limited disease, because recurrent DFSPs have a tendency to grow deeper. Excision with wide margins leads to improvement of the recurrence rate. When the surgical margins are at least 3cm and there is a three-dimensional resection that includes skin, subcutaneous tissue and the underlying fascia, the rate of recurrence is 20%. It is necessary to be mentioned that in cases where the underlying bone structures are too close to the lesion, the periosteum and the portion of the bone may also need to be removed in order to achieve negative deep surgical margins. However, the use of wide margins leads, usually, to the need of reconstructive surgery [36]. In the most recent study [22] margins were positive in primary DFSP in 11.8% cases, while margins were positive in 14.6% of cases with recurrent DFSP [34]. Among all these cases, reconstructive surgery was needed in 30%, mainly in cases where the lesion was on the head or neck [34]. In case of margins less than 2cm, the rate increases to 40%. On the contrary, in cases where the margins were more than 5cm, the rate of recurrence was less than 5% [11,27]. To summarize, complete surgical resection is the optimal treatment for DFSP. However, the minimum resection margin needed in order to achieve perioperatively no evidence of disease is still undefined. There are several groups of researchers that have studied the different surgical techniques and their results are presented in Table 3. According to these studies, DFSP can be managed in a successful way with wide local excision. In case of positive margins or recurrence, resection with or without adjuvant radiotherapy is indicated. MMS seems to be very useful in cases where wide excision is not feasible. DFSP is considered as radio-

Table 3. Results of wide local excision of dermatofibrosarcoma protuberans

Group	No. of patients	Local recurrence (%)	Follow-up, median
Bowne et al. [17]	159	21	32 months
	60		
Fiore et al. [22]	218	3	5 years
		4.25	10 years

sensitive tumor [16]. However, adjuvant radiotherapy is not extensively studied, even though it was found that has successfully contributed to local tumor control [32]. In the study of MD Anderson Cancer Center in 1998 the estimated rate of local control in 19 patients who received radiotherapy as adjuvant to surgical resection was 95% at 10 years [37].

As already mentioned, DFSP is characterized by a translocation (COL1A1-PDGF) and the fusion protein which derives from this translocation is PDGF- β -like protein. *In vitro* evidence suggests that when this fusion protein was expressed in a stable NIH3T3 cell line, it caused morphological transformation and increased the growth of cells [34]. As a result, use of tyrosine kinase inhibitors could lead to a new pharmaceutical approach.

On October 19, 2006, the U.S. Food and Drug Administration (FDA) granted approval to imatinib mesylate (Gleevec, Novartis Pharmaceuticals) as a single agent for the treatment of DFSP, among other malignancies. The approved new indication and recommended dosage for Gleevec are: Gleevec is indicated for the treatment of adult patients with unresectable, recurrent and/or metastatic DFSP. Recommended dose: 800 mg/day [38].

Imatinib mesylate, an orally administered tyrosine kinase breakpoint cluster region-abeloproteinemia (BCR-ABL) inhibitor, which also affects ABL-related kinase, KIT, platelet-derived growth factor β (PDGF β), and PDGF receptor- α , has been very effectively used to treat gastrointestinal (GI) stromal tumors (GISTs) and chronic myelogenous leukemia. Coincidentally, the stimulation of expression of PDGFR β on the cell surface of many DFSP tumors has been noted, related to pathogenetic expression of the fusion gene collagen type 1 alpha 1 (COL1A1)-PDGF β . It has been reported that more than 90% of DFSPs possess supernumerary ring chromosomes or a unique translocation involving chromosomes 17 and 22 *t*(17;22)(22;q13), which fuse the COL1A1 gene on chromosome 17 with the PDGF β -chain gene on chromosome 22. PDGF β , a tissue growth factor,

Table 4. Immunohistochemical and cytogenetic markers of dermatofibrosarcoma protuberans (DFSP)

Markers	Method	Comments
CD34 and vimentin	Immunostaining	Helps in diagnosis of DFSP
CD117	Immunostaining	Used only for GIST susceptibility to imatinib
Apolipoprotein B	Immunostaining	New marker for diagnosis of DFSP
COL1A1-PDGF β	FISH	Confirms probable susceptibility to imatinib; diagnosis of DFSP if loss of CD34 observed
<i>t</i> (17;22)	RT-PCR	Confirms probable susceptibility to imatinib; diagnosis of DFSP if loss of CD34 observed

encodes the β -chain of PDGF, which is a ligand for tyrosine kinase PDGFR located on the cell surface. The aberrant fusion gene, COL1A1-PDGF β , is under the control of the COL1A1 promoter, with the resulting fusion protein processed into mature PDGF β in DFSP cells, leading to autocrine stimulation of PDGF β R on the surface of DFSP cells and subsequent cellular proliferation and tumor growth. As imatinib mesylate is an orally active selective tyrosine kinase inhibitor with activity against specific kinases, its ability to inhibit PDGFR protein-tyrosine kinase attracted interest in this drug for the treatment of DFSP (Table 4) [39].

Imatinib inhibits the activity of the PDGF β protein that causes increased proliferation by attaching to the ATP binding site needed for auto-phosphorylation of tyrosine kinases. This binding decreases the enzymatic activity in DFSP cells and inhibits their ability to divide and grow. Furthermore, the reduced enzymatic activity of imatinib has been shown to induce apoptosis in tumor cells. Both *in vitro* and *in vivo* data have shown that blocking of the PDGF β autocrine loop in DFSP with imatinib leads to reversible reduction of DFSP cell line growth. This indicates that the activation of the PDGF β R tyrosine kinase is essential to the pathogenesis of the disease and vital for tumor cell growth. Investigators have observed DFSP lesions with an increase in the hypocellular and acellular areas post-imatinib therapy, leading many to believe in the apoptosis theory as the mechanism responsible for the decrease of tumor size. Other theories postulate that imatinib may change the phenotype of DFSP cells reducing proliferation and tumor size, thus making the lesion more amenable to complete surgical resec-

tion [39].

One of the largest studies with imatinib in DFSP patients took place in 2005 [40] and involved cases of both metastatic and locally advanced DFSP. The dose was 400 mg twice daily, and the drug was well tolerated by the patients. All patients with locally advanced disease had partial (50%) or complete remission to imatinib. Patients with metastatic disease had no clinical response to imatinib (one responded for the first 6 months, but subsequently developed disease progression, while another one died of complications of a pathological fracture 21 days after starting therapy with imatinib) [34]. In locally advanced disease, imatinib has shown impressive activity, with limited toxicity. The dose varies from 400mg/day to 400mg/twice a day. It is suggested that one could start at a lower dose and, in case of no response, increase the dose to 400mg/twice a day [34].

In a pooled analysis of two phase II trials published in 2010 the largest prospectively collected cohort of locally advanced/metastatic DFSP was reported and the excellent activity of imatinib in this selected group of poor-prognosis patients was confirmed: one European trial (EORTC) with 14-week progression-free rate as the primary end point, and the other one in North America (SWOG) with confirmed objective response rate as the primary end point. In the EORTC trial, confirmation of *PDGFB* rearrangement was required, and surgery was undertaken after 14 weeks if feasible. The SWOG study confirmed *t(17;22)* after enrollment.

DFSP response rate of 46%, 1-year progression-free survival rate of 58%, and median time to progression of 1.7 years with treatment with

imatinib was demonstrated. Although there were notable differences in trial design, the observed response rate at 14 to 16 weeks and progression-free survival rate at 1 year were remarkably similar between the studies, suggesting that a daily dose of 400 mg has similar efficacy to 800 mg daily.

Most of the previously reported patients had been treated with doses of imatinib exceeding 400 mg daily. We have also found that DFSP-fibrosarcomatous (FS) retains sensitivity to imatinib, although responses may be less durable. DFSP-FS tumors lacking *t(17;22)* do not respond to imatinib, suggesting misdiagnosis of disease or loss of tumor dependence on the *PDGFR* signaling pathway. Therefore, testing for the presence of *t(17;22)* in DFSP-FS before therapy with imatinib, especially in the neoadjuvant setting, has been advocated [41]. The most common adverse events noted were fluid retention/edema, anemia, fatigue, nausea, vomiting, skin toxicity, thrombocytopenia, neutropenia, and diarrhea [42]. Imatinib has already been used in cases of GIST and it is proved that is of benefit to patients with surgically resected large and histologically aggressive GISTs [43]. This is the reason why many researchers believe that imatinib may be effective in cases of very large tumors that require extensive and potentially disfiguring surgery [24,31,44].

Conclusion

DFSP is a tumor that rarely generates distant metastases, and it occurs only after many years of tumor progression. Wide local excision is the

Table 5. Response to imatinib

Patient No.	Stage	Best response	Duration of imatinib (days)	Duration of response to imatinib (days)	Duration of follow-up (days)
1	Locally advanced	Partial response (Disease free after surgical resection)	698	685	845
2	Locally advanced	Partial response (Disease free after surgical resection)	62	62	699
3	Locally advanced	Partial response (Disease free after surgical resection)	141	141	572
4	Locally advanced	Complete response	457	457	536
5	Locally advanced	Partial response (Disease free after surgical resection)	139	139	258
6	Locally advanced	Complete response	188	188	267
7	Locally advanced	Complete response	146	146	225
8	Locally advanced	Complete response	88	88	88
9	Metastatic	Partial response	198	198	383
10	Metastatic	Stable disease (patient deceased after day 32)	21	N/A	32

N/A: not available

gold standard treatment and a policy of re-excision to obtain negative margins should always be followed. One of the most challenging areas is the head and neck, with increased rate of local failure, due to critical structures and aesthetic difficulties in reconstruction [45]. Several published reports indicate that imatinib mesylate has significant activity against DFSP. The largest study was report-

ed in 2005 and its results provided a lot of information about recurrence free survival of patients who undergo surgery and chemotherapy (Table 5) [40]. DFSP metastasizes haematogenously to the lung (75%) [3,4,11,45]. Twenty-five percent develop regional lymph nodes metastasis. Metastases to brain, bones and heart occur rarely.

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