Actas Dermosifiliogr. 2007;98:77-87

REVIEW ARTICLE

Dermatofibrosarcoma Protuberans*

O Sanmartín, B Llombart, JA López-Guerrero, C Serra, C Requena, and C Guillén
Servicio de Dermatología, Instituto Valenciano de Oncología, Valencia, Spain

Abstract. Dermatofibrosarcoma protuberans (DFSP) is a soft tissue neoplasm of intermediate malignancy that is initially localized to the skin from where it can invade deep structures (fat, fascia, muscle and bone). It is the most frequent fibrohistiocytic tumor, comprising approximately 1.8% of all soft tissue sarcomas and 0.1% of all cancers. It has an estimated incidence of 0.8-5 cases per one million persons per year. Treatment of localized disease consists in complete surgical excision of the lesion by conventional surgery with wide margins (> 3 cm) or by micrographic Mohs surgery. Although the cases of metastatic DFSP do not reach 5% of the total, almost all of them appear after previous local relapses. The prognosis for metastatic cases is very poor with a survival of less than 2 years following detection of metastatic disease. Patients with locally advanced DFSP are not candidates for an initial radical surgical therapy therefore neoadyuvant treatment is required prior to surgery in order to reduce tumor burden. In this regard, chemotherapy and radiotherapy have not been highly efficacious so it is necessary to consider new alternatives. The demonstration of the oncogenic power of the translocation COL1A1-PDGFB in DFSP has allowed the successful introduction of drug therapy with antagonists of the PDGFB receptor for metastatic or locally advanced cases.

Key words: dermatofibrosarcoma protuberans, Mohs surgery, COL1A1-PDGFB, imatinib, RT-PCR.

DERMATOFIBROSARCOMA PROTUBERANS

Resumen. El dermatofibrosarcoma protuberans (DFSP) es una neoplasia de partes blandas de malignidad intermedia, localizada inicialmente en la piel, desde donde invade tejidos más profundos (grasa, fascia, músculo y hueso). Se trata del tumor fibrohistiocitario más frecuente, constituyendo aproximadamente el 1,8 % de todos los sarcomas de partes blandas y un 0,1 % de todos los cánceres. Su incidencia se ha estimado entre 0,8-5 casos por millón de habitantes y año. El tratamiento de la enfermedad localizada consiste en la resección quirúrgica completa de la lesión, bien mediante cirugía convencional con margen amplio (> 3 cm) bien mediante cirugía micrográfica de Mohs. Aunque los casos de DFSP metastásico no llegan al 5 % del total, prácticamente todos ellos aparecen tras recaídas locales previas. El pronóstico de los casos metastásicos es muy pobre, con menos de 2 años de supervivencia tras la detección de la enfermedad metastásica. Los pacientes de DFSP con tumores localmente avanzados no son susceptibles de tratamiento quirúrgico radical de inicio, por lo que se precisa tratamiento neoadyuvante previo a la cirugía para disminuir el tamaño tumoral. En este sentido, la quimioterapia y la radioterapia se han mostrado poco eficaces, por lo que se hace necesario contar con nuevas alternativas terapéuticas. La demostración del poder oncogénico de la traslocación COL1A1-PDGFB en el DFSP ha permitido introducir con éxito el tratamiento farmacológico con inhibidores del receptor del PDGFB en los casos metastáticos o localmente avanzados.

Palabras clave: dermatofibrosarcoma protuberans, cirugía de Mohs, COL1A1-PDGFB, imatinib, TI-PCR.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare soft-tissue tumor of cutaneous origin with an intermediate level of malignancy. Although metastasis only occurs in exceptional cases, morbidity is high due to the high local invasive capacity of the tumor and the high rate of recurrence following surgical removal. The first descriptions of this entity were made in 1924 by Darier and Ferrand,[1] who

Correspondence:
Onofre Sanmartín Jiménez
Servicio de Dermatología
Instituto Valenciano de Oncología
Profesor Beltrán Báguena 8, 46009 Valencia, Spain
E-mail: osanmartinj@gmail.com

Manuscript accepted for publication December 19, 2006.

*This article was funded in part by a grant from the regional government of Valencia (Generalitat Valenciana), Spain (grant GV06/274).

designated it progressive and recurrent dermatofibroma. One year later, based on the tendency of the tumor to develop protruding nodules, Hoffman[2] coined the term dermatofibrosarcoma protuberans. Most early descriptions of DFSP considered its clinical characteristics and the tendency for recurrence following surgical excision. In 1962, Taylor and Helwig,[3] in a review of 115 cases, described in detail the histological characteristics of the lesion and characterized a fibroblastic growth appearing as a low-grade sarcoma in which the tumor cells were organized in fascicles with a spiral or cartwheel arrangement. In 1992, the first descriptions were provided of DFSP immunopositivity for CD34,[4] and this continues to be the main immunohistochemical marker for diagnosis of the tumor, particularly when associated with the absence of immunostaining for factor XIIIa in most cases.[5] In 1997, it was demonstrated that many cases of DFSP display a characteristic t(17;22) translocation.[6] The breakpoint in this t(17;22) translocation normally affects exon 2 of the gene encoding the B chain of platelet derived growth factor (PDGFB), located on chromosome 22, leading to fusion with the gene encoding the α1 chain of collagen I (COL1A1) located on chromosome 17. In all cases, the COL1A1 gene is expressed at high levels, acting as an inducer of gene transcription. The result of this translocation is the formation of a COL1A1-PDGFB fusion protein, which is processed extracellularly to produce fully mature, functional PDGFB. The PDGF that is released is able to stimulate mitogenesis via activation of its receptor. Thus, the product of the COL1A1-PDGFB fusion leads to activation of the PDGFB receptor via autocrine and paracrine production of its functional ligand.

In recent years a number of advances have been made in the understanding of the cytogenetics and immunohistochemical characteristics of this tumor, and specific techniques have been introduced for diagnosis, staging, and treatment to allow effective control of the disease in the majority of patients. The aim of this article is to review and update information on the incidence, epidemiology, histology, immunohistochemical findings, cytogenetics, prognosis, and treatment of this tumor. Special emphasis will be placed on description of the molecular biology of the tumor and the treatment options through Mohs micrographic surgery and the use of PDGF receptor inhibitors.

Epidemiology

DFSP is a rare tumor. Its incidence in the United States of America has been calculated between 0.8 and 4.5 cases per million individuals per year.[7-9] A recent epidemiological review reported an incidence of 4.2 cases per million individuals per year.[10] This rate represents 0.1% of all cancers and 1% of all soft-tissue sarcomas.[11] However, taking into account only cutaneous tumors, DFSP is the most common sarcoma of cutaneous origin.

DFSP has been described in all races. The incidence of DFSP in black individuals has been calculated to be approximately twice that of white individuals, with no known explanation for this difference.[10] The pigmented variant of DFSP (Bednar tumor) also occurs predominantly in black patients.[12]

Most large patient series have shown a homogeneous sex distribution, with a slight bias towards men. Rutgers et al[13] undertook a literature review of 902 cases and found a ratio of men to women of 3:2. However, more recently, in an epidemiological review of 2885 cases recorded in the National Cancer Institute databases, Criscione et al[10] observed a higher rate in women.

DFSP can appear at any age, although it is much more frequent in individuals aged between 20 and 50 years. Cases have been described ranging from congenital disease to cases in patients older than 90 years.[14,15] Few cases of DFSP have been described in children, although as it is an asymptomatic tumor that is usually diagnosed late as a result of its slow growth, many cases diagnosed in adults begin during childhood.[7] The proportion of pediatric cases in published case series of DFSP ranges between 6% and 20%.[3,16,17] It should be taken into account that giant cell fibroblastoma (GCF) is currently considered to be the juvenile form of dermatofibrosarcoma. GCF was first described in 1982 as an early childhood tumor characterized histologically by a storiform spindle-cell growth with myxoid areas and the typical presence of multinucleate giant cells surrounding pseudovascular spaces.[18] Since their description, both forms had been considered separate entities until in 1989 Shmookler et al[19] described various cases of GCF with clinical and histological findings consistent with DFSP. This relationship between the 2 tumors has subsequently been confirmed by the description of numerous cases that share findings consistent with DFSP and GCF, both from a clinical and an immunohistochemical and cytogenetic perspective.[20] In a recent review of skin cancer in patients aged less than 25 years, DFSP-GCF was the third most frequent condition, found in 13% of cases, behind melanoma and basal cell carcinoma.[21]

A history of trauma as a possible etiological factor in DFSP is the subject of some debate. Such events might favor the development of the tumor, since a history of trauma is reported in 10% to 20% of cases.[3,11,22] Likewise, cases of DFSP have been described in which tumors are located on the sites of surgical scars,[23] trauma scars,[24] burns,[25] radiodermatitis,[26] vaccination scars,[27] and sites of central venous lines.[28]

DFSP is preferentially located on the trunk. In 40% to 50% of cases the tumor is located in this area, generally on the chest and shoulders; in between 30% and 40% of cases the tumor is located in the proximal portion of the

limbs (more often on the arms than the legs); and in 10% to 15% of cases DFSP affects the head and neck, generally the scalp and supraclavicular area. Treatment is more difficult when the tumor is located on the head and neck, and this may explain the increased rate of recurrence compared with other sites.[29] When located on the scalp, invasion of the periosteum occurs in up to 25% of cases.[30] DFSP located in peripheral areas is rare, especially in adults. In a review of the literature, Gloster[11] reported that DFSP of the hands and feet represented only 0.01% of cases. However, it has been reported that childhood DFSP has a greater tendency towards peripheral localization. Rabinowitz et al[31] performed a review of 27 previously published cases of childhood DFSP and found that 14.8% were located on the hands or feet. In 1998, Martin et al[17] reviewed 140 published cases of childhood DFSP and demonstrated that the only difference between the childhood and adult forms of the disease was the higher frequency of peripheral localization in children. This tendency in cases of DFSP occurring in childhood has not been confirmed by a similar tendency toward peripheral localization in reviews of cases of GCF,[18] considered the pediatric form of DFSP; consequently, the trend towards peripheral localization of DFSP in childhood can not be definitively confirmed. In fact, of the 150 pediatric cases of DFSP published to date, localization in peripheral sites was reported in less than 9%.

Clinical Characteristics

DFSP is a slow-growing, indolent tumor, and as a consequence, patients tend to consult their doctor at a late stage. The clinical appearance of DFSP depends on the time since onset. It tends to present initially as a discrete asymptomatic plaque with a violaceous, reddish-brown, or pink appearance, with a hard consistency and fixed to the skin but not deep layers (Figure 1). Over time, the plaque can remain stable for an extended period, grow slowly, or enter a phase of rapid growth with the development of multiple nodules, from which its name protuberans is derived (Figures 2 and 3). In exceptional cases, DFSP manifests from onset as a single or multiple firm reddish-purple intradermal nodules.

In the initial stages of DFSP, when the characteristic protruding appearance of the lesion has not yet been acquired, diagnostic errors are common, with the lesion being interpreted as a hypertrophic scar. Consequently, Martin et al[32] studied the clinical profiles of early stages of DFSP. They distinguished 3 forms of clinical presentation of nonprotruding DFSP: *a)* 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; *b)* atrophoderma-like, characterized by a soft depressed white or brown plaque that appears similar to atrophoderma or anetoderma; and *c)* 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

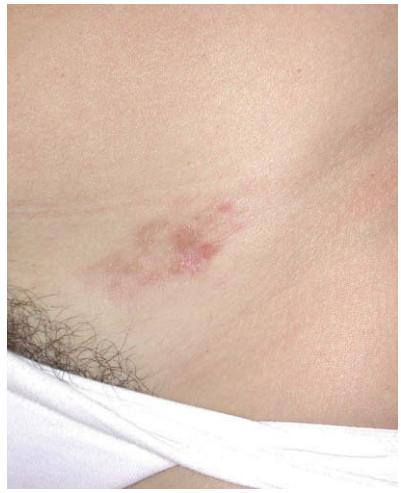

Figure 1. Initial phase of dermatofibrosarcoma. Infiltrated brownish plaque with small nodules on its surface.

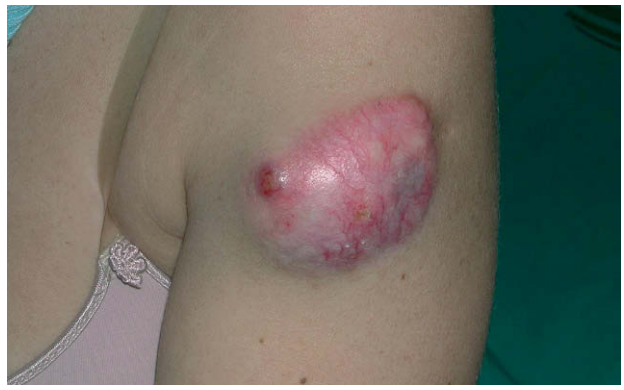

Figure 2. Dermatofibrosarcoma in the proliferative phase. Rapidly growing nodule on the arm.

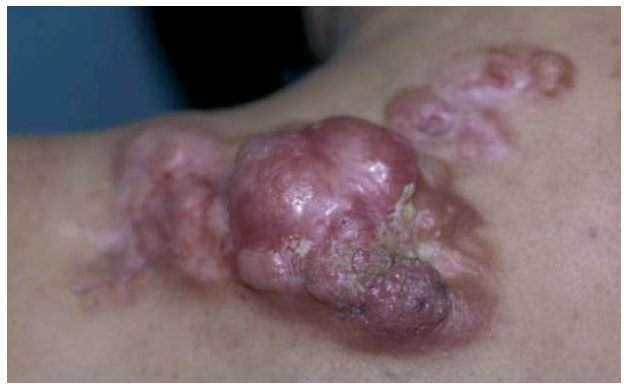

Figure 3. Dermatofibrosarcoma protuberans. Multiple protruding nodules on a scar from previous excision.

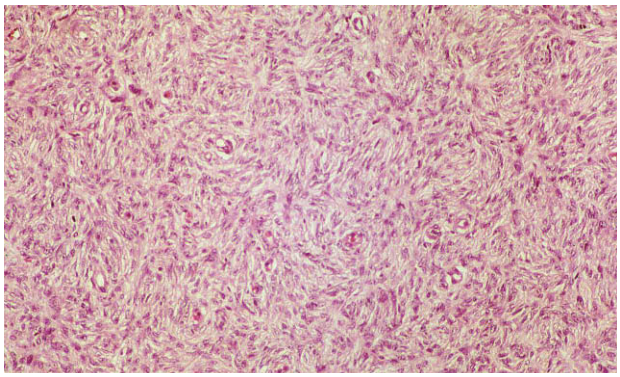

Figure 4. Low-magnification view of dermatofibrosarcoma protuberans. Spindle-cell growth without atypical cells in a classic storiform arrangement occupying the entire dermis. (Hematoxylin-eosin, ×20.)

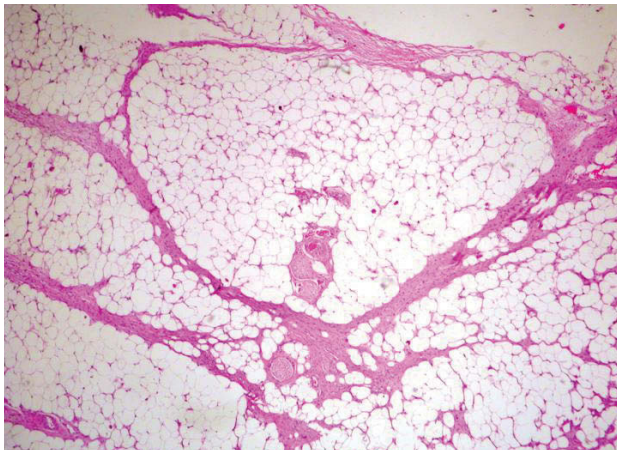

Figure 5. Invasion of the subcutaneous cellular tissue through tentacle-like tumor projections that extend through the septa. (Hematoxylin-eosin, ×10.)

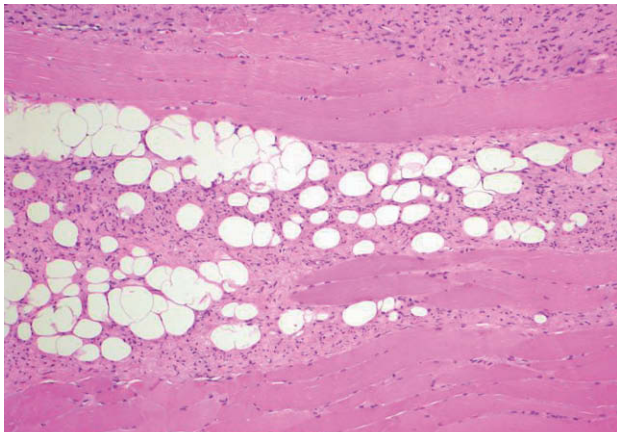

Figure 6. Invasion of striated muscle by dermatofibrosarcoma protuberans. (Hematoxylin-eosin, ×20.)

angioma. According to those authors, the most common presentation in adults is that of a large plaque with multiple nodules on its surface. In children, nonprotruding forms such as morphea-like plaques, and congenital cases, such as atrophoderma-like, are more common, particularly when the lesions are located on the trunk. The size of the lesion at the time of diagnosis is usually between 2 and 5 cm in diameter, although they often pass unnoticed by the patients and can reach 25 cm.

The lesions adopt an invasive growth pattern and palpation reveals adhesion to the surrounding skin. Older or recurrent lesions can display invasion of deep structures such as the fascia, muscle, periosteum, or bone.

Histology

The histological appearance of DFSP is of a well-differentiated fibrosarcoma. The tumor is initially localized to the dermis and is composed of a dense growth of monomorphous fusiform cells with a large elongated nucleus and generally with little pleomorphism and a low mitotic index. There is generally very little stroma, with intercellular deposits of collagen and small capillaries. The spindle cells are organized in irregularly linked fascicles with a storiform arrangement (Figure 4). In some areas the cells are arranged radially in a cartwheel pattern around a central acellular area composed of collagen; this was reported by Taylor and Helwig[3] as being of great diagnostic value.

The main histological characteristic of DFSP is its capacity to invade surrounding tissues to a considerable distance from the central focus of the tumor. The cellularity is greater in the central zone than in the peripheral part of the tumor, where the edges invade the surrounding dermis and subcutis. The tumor cells invade the subcutaneous cellular tissue in the form of tentacle-like projections via the septa and fat lobules (Figure 5). These tumor extensions contain few cells and can at first sight appear similar to normal fibrous tracts. This makes it difficult to determine the true extent of the lesion and can be the cause of recurrence following excision with apparently wide margins. Involvement of the fascia, underlying muscles and periosteum, and the bone is a late event (Figure 6).

The histological differential diagnosis should be carried out essentially with other tumors with a fibrohistiocytic appearance, such as fibrosarcoma, malignant fibrous histiocytoma, and dermatofibroma. Fibrosarcomas are very rare in the skin and tend to be found in deeper sites; they are also composed of a spindle-cell growth with marked pleomorphism and a high mitotic index. The organization of the cell fascicles usually follows a horseshoe or herringbone pattern rather than a storiform one.

During its initial plaque stages, DFSP can appear similar to a cellular or fibrous dermatofibroma. Sometimes, cellular dermatofibroma can exhibit a storiform pattern and invade

the subcutaneous cellular tissue, hindering differential diagnosis with DFSP. However, when dermatofibroma invades the fat it does so with either a radial pattern following the septa of the subcutis or with a deep compressive pattern. In contrast, DFSP invades the fat in 30% of cases with a honeycomb pattern, whereas in 70% of cases it does so with a multilayered pattern involving spindle cell layers oriented parallel to the skin surface.[33,34]

Immunohistochemistry

At the beginning of the 1990s, various studies found that the CD34 antigen is expressed in 50% to 90% of DFSP, a finding that is not observed in other fibrohistiocytic tumors that can sometimes be confused with DFSP, such as dermatofibroma, malignant fibrous histiocytoma, pediatric myofibromatosis, fibrosarcoma, hypertrophic scars, or keloids.[35,36] Since its introduction in clinical practice, expression of CD34 has been considered characteristic and fundamental for the differential diagnosis of DFSP. However, over time it has come to be noticed that CD34 is also expressed by other sarcomas, such as inflammatory myofibroblastic sarcoma (inflammatory fibrosarcoma), myofibrosarcoma, angiosarcoma, and epithelioid sarcoma; consequently, CD34 should now be considered less specific for DFSP. In recent years, various studies have shown that this marker can even be expressed by some benign fibrohistiocytic lesions, such as solitary fibrous tumor,[37] sclerotic fibroma,[38] superficial acral fibromyxoma,[39] cellular digital fibromas,[40] and nuchal-type fibroma,[41] and even some dermatofibromas can express this marker.[42]

Factor XIIIa is very useful in the differential diagnosis between DFSP and cellular fibrous histiocytomas, since it is usually negative in DFSP. However, not all fibrous histiocytomas express factor XIIIa, and as a consequence, new immunohistochemical panels have been described in recent years for the differential diagnosis of the 2 entities, including stromelysin III, apolipoprotein D, and CD163.[42-44] Like factor XIIIa, these 3 markers tend to be positive in dermatofibromas and negative in DFSP.

Histological Variants

There are different histological variants of DFSP, some of which, like the fibrosarcomatous form, have a worse prognosis, and their presence must be assessed in the histological study.

Myxoid Dermatofibrosarcoma

DFSP often contains small areas of myxoid degeneration. However, sometimes the predominant histological pattern throughout the tumor is myxomatous. Myxoid DFSP is characterized by the presence of moderately cellular areas made up of stellate or fusiform cells with abundant accumulation of hyaluronidase-sensitive mucin in the intercellular space. The tumor tends to be well vascularized and areas of classic DFSP with dense cellularity and a storiform pattern can be found within the thickness of the lesion. Myxoid DFSP does not differ from conventional DFSP in terms of clinical characteristics or prognosis, making its recognition of use only in the differential diagnosis with other myxoid sarcomas such as myxoid fibrosarcoma, inflammatory myxofibrosarcoma, and myxoid liposarcoma.

Pigmented Dermatofibrosarcoma (Bednar Tumor)

Pigmented dermatofibrosarcoma was described by Bednar in 1957. It is a storiform spindle-cell tumor that contains a population of varying numbers of melanin-producing dendritic cells. This cell population may arise from dermal melanocytes that colonize the tumor. Depending on the amount of melanin in the lesion, it can become clinically pigmented, although this is sometimes only a microscopic finding. It is calculated that 1% of DFSP are pigmented.

Fibrosarcomatous Dermatofibrosarcoma

The fibrosarcomatous variant of DFSP is considered a rare lesion. The incidence is fibrosarcomatous changes in DFSP is not known with any accuracy but has been reported to be between 3% and 10% of all cases of DFSP, depending on the patient series.[45,46] It is characterized histologically by a dense growth of fusiform cells organized in fascicles that are arranged in a horseshoe or herringbone pattern. The tumors contain abundant, moderately atypical cells with an elevated mitotic index (Figure 7). Areas of conventional DFSP without atypical cells can be found accompanying the fibrosarcomatous regions. The proportion of fibrosarcomatous areas ranges between 30% and 50% of the tumor. It should be taken into consideration that these transformed areas show little or no expression of CD34, further hindering diagnosis. This histological variant is characterized by a more aggressive behavior, with a higher rate of local recurrence following surgery and an increased risk of distant metastasis.[47] It has been suggested that this transformation in DFSP is favored by prior recurrence of the tumor following inadequate surgery,[46] although this has not been confirmed in all case series.[45,47] The appearance of fibrosarcomatous areas in DFSP is no more than a progression of the histological grade in the sarcoma, possibly due to the appearance of new genetic alterations in the tumor, such as the presence of new copies of the COL1A1-PDGFB translocation[48] or mutations in p53,[47,49] which

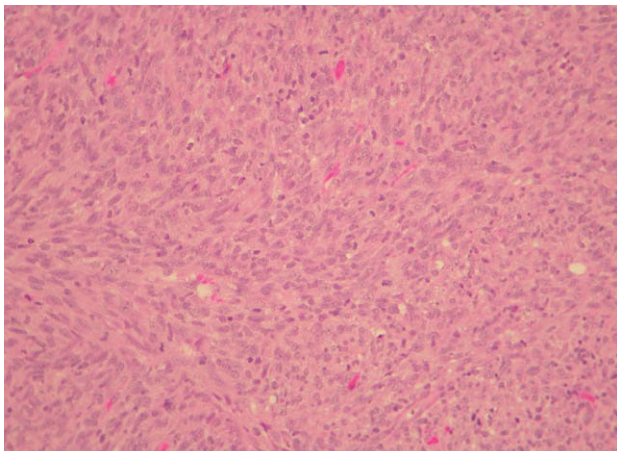

Figure 7. Dermatofibrosarcoma protuberans with fibrosarcomatous areas. Spindle-cell growth organized in fascicles with a herringbone pattern and with numerous mitotic figures and atypical nuclei. (Hematoxylin-eosin, ×20.)

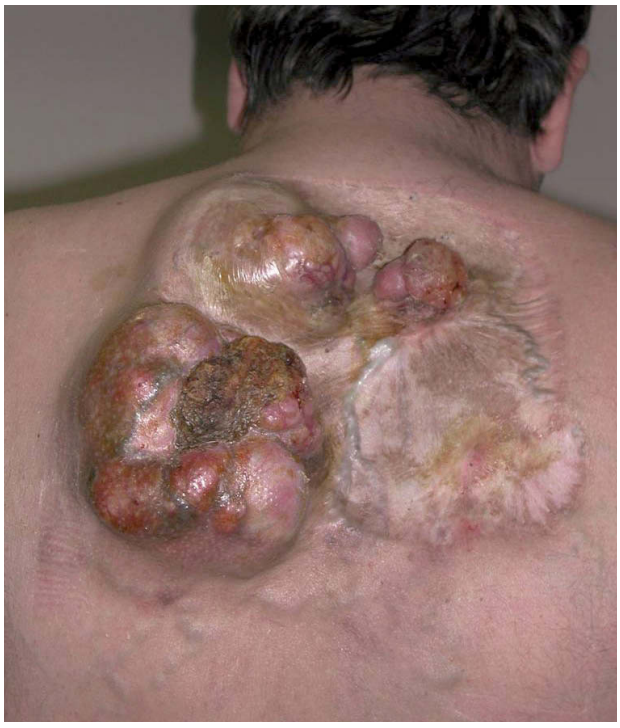

Figura 8. Dermatofibrosarcoma protuberans with fibrosarcomatous transformation. Large recurrent tumor on the back located on the site of scars from previous surgical excisions.

favor a more aggressive biological behavior, with tumors that grow much more rapidly and often generate metastases (Figure 8).

Atrophic Dermatofibrosarcoma

Atrophic dermatofibrosarcoma is a histological variant characterized by a marked atrophy in the dermis overlying the tumor, reducing its thickness by more than half. Clinically, it is characterized by the appearance of a depressed, generally soft plaque that is diagnosed clinically as anetoderma, atrophoderma, or morphea. Some 30 cases have been reported, most of them on the trunk, although in children it is preferentially located on the limbs.[50] The prognosis of atrophic DFSP does not differ from that of conventional types and it is probably the result of secretion of fragments of COL1A1 of a certain length by the tumor cells, leading to digestion of the dermis by collagenases.[51]

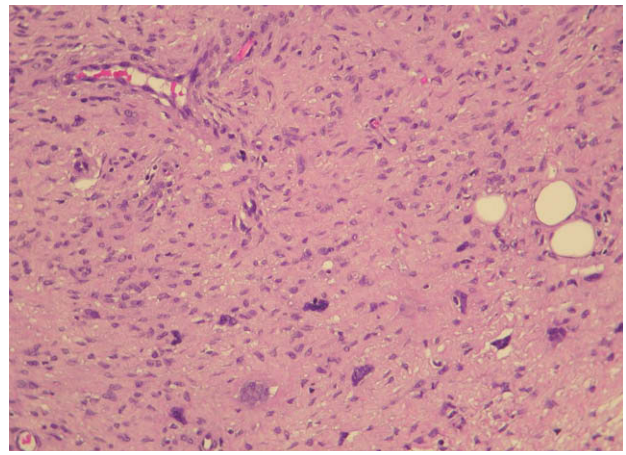

Figura 9. Dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma. (Hematoxylin-eosin, ×20.)

Dermatofibrosarcoma With Areas of Giant Cell Fibroblastoma

As mentioned, GCF is a childhood variant of DFSP. Nevertheless, some cases of adult DFSP display areas of the tumor with giant cells surrounding sinusoidal spaces characteristic of GCF (Figure 9).

Other Histological Variants of DFSP

In addition to those mentioned, different histopathological variants of DFSP have been described, and while their recognition is of value for differential diagnosis with other tumors they do not have added prognostic value. These variants are sclerosing DFSP,[52] DFSP with myoid areas,[53] and DFSP with granular cells.[54]

Cytogenetics and Molecular Biology of DFSP

Since 1990 it has been known that supernumerary ring chromosomes are present in some cases of DFSP.[55] Subsequently, use of fluorescence in situ hybridization

(FISH) revealed that the ring chromosome in DFSP contained sequences from chromosome 17.[56] A combination of FISH and comparative genomic hybridization also revealed the involvement of chromosome 22 in the formation of the ring chromosome, with low levels of amplification of the 17q22-qter and 22q10-q13.1 regions. Since then, the presence of ring chromosomes derived from chromosome 22 containing sequences from chromosomes 17 and 22 has been considered characteristic of dermatofibrosarcoma.[57] These chromosomes can also be found in cases of GCF. It was first reported in 1995 that there was a t(17;22) translocation involved in DFSP.[58] Subsequently, 4 new cases of DFSP—3 in children and 1 in an adult—were described with various forms of t(17;22) in the ring chromosomes.[59] Cytogenetics and FISH revealed that in most cases of DFSP the ring and linear der(22) chromosomes contain sequences from chromosome 22 between the centromere and the 22q13.1 band, as well as sequences from chromosome 17 between 17q21/22 and 17qter. A combination of FISH and molecular biology has helped to identify the fusion of PDGFB at 22q13.1 with COL1A1 (17q/22).[6]

In these studies it has been demonstrated that more than 90% of cases of DFSP carry the t(17;22) translocation; however, since the studies have always involved small case series, the true frequency of the translocation remains to be demonstrated. The breakpoint in the t(17;22) translocation usually affects exon 2 of the PDGFB gene, located on chromosome 22, and leads to fusion with COL1A1 located on chromosome 17. In the case of COL1A1, various breakpoints affecting different exons of the gene have been described. In all cases, the COL1A1 gene is expressed at high levels, acting as an inducer of gene transcription.[60]

Following transcription, the COL1A1-PDGFB fusion protein is processed extracellularly to produce fully mature, functional PDGFB, which is able to act as a mitogen via activation of its receptor.[61] Thus, the product of the COL1A1-PDGFB fusion leads to activation of the PDGFB receptor via autocrine and paracrine production of its functional ligand. This receptor is essentially composed of 3 structural domains: an extracellular ligand-binding domain, a transmembrane activation domain, and a cytoplasmic domain with tyrosine kinase activity, which, in response to ligand binding, triggers an intracellular signaling cascade affecting cellular processes such as proliferation, chemotaxis, and apoptosis.

The observation of aberrant expression of PDGFB in DFSP as a consequence of the t(17;22) translocation suggests that the use of specific tyrosine kinase inhibitors such as imatinib could prove useful in cases of DFSP that are not suitable for treatment with radical surgery, thereby offering a therapeutic alternative. In fact, in isolated cases of DFSP in which imatinib has been used, high response rates have been obtained, supporting the hypothesis that the cells of DFSP depend on the aberrant expression of PDGFRB for proliferation and cell survival.[62]

The presence of the COL1A1-PDGFB fusion gene in DFSP can be demonstrated with molecular biology techniques such as reverse-transcriptase polymerase chain reaction (RT-PCR) using RNA extracted from tumor samples.

This procedure is highly sensitive and specific and represents a very useful tool in the differential diagnosis of DFSP with other tumors that have similar histology (Figure 10).

The problems associated with analyzing translocation by RT-PCR in paraffin-embedded tissue samples can be resolved through the use of FISH with specific probes for the 2 genes implicated in the lesion; this is the most easily applied technique for use in paraffin-embedded samples.

Course, Treatment, and Prognosis

DFSP is a locally aggressive tumor characterized by a low rate of metastasis and high local invasion. Consequently, the treatment of choice is surgery. Between 85% and 90% of DFSP display a low degree of malignancy and are characterized by slow invasive growth with little likelihood of distant metastasis, but with a high capacity for local destruction and a high rate of recurrence following surgery. However, in 10% to 15% of cases, DFSP may undergo fibrosarcomatous transformation, which increases the aggressiveness of the lesion; this is more common in cases of multiple recurrence, and consequently, complete resection of the lesion from the outset is important. Nevertheless, achieving local control of the tumor is difficult, since DFSP recurs following conventional surgery in up to 30% of cases. This high rate of recurrence is explained by the eccentric growth of the tumor when it invades the subcutaneous cellular tissue. At this level, the tumor invades in the form of tentacle-like projections at a distance from the initial focus. These projections can pass clinically unnoticed and can remain occult if an exhaustive histological study of the surgical margins is not performed.

Excision with wide margins leads to a notable reduction in the rate of recurrence.[63] Thus, when the surgical margins are at least 3 cm, the rate of recurrence is 20%, whereas if

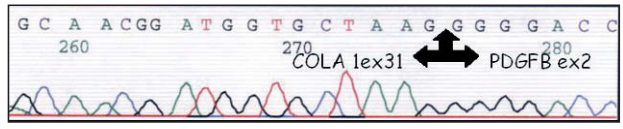

Figure 10. Sequencing of the COL1A1-PDGFB translocation.

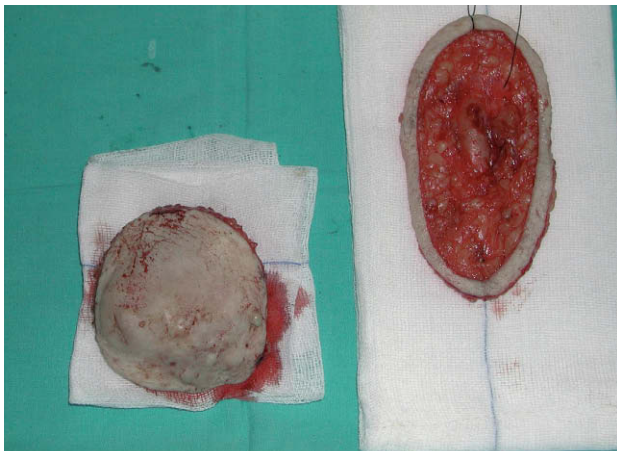

Figure 11. Slow Mohs micrographic surgery in dermatofibrosarcoma protuberans. Elimination of the detectable tumor (debulking) and preparation of the area for analysis of the margins by horizontal paraffin sections.

they are less than 2 cm, the rate increases to 40%.[64] Those series in which margins of 5 cm were used reported rates of recurrence of less than 5%.[65]

Local recurrence generally appears in the first 3 years following initial surgery, although cases have also been described after a number of years, indicating that long-term follow-up should be carried out. The main drawback of conventional surgery with wide margins is the high morbidity associated with excision of large areas of healthy tissue and the risk of eccentric subcutaneous extension of the tumor passing unnoticed.

Mohs micrographic surgery allows complete examination of the margins whilst sparing the maximum amount of healthy tissue. This has made it the surgical technique of choice for the treatment of DFSP. This is the technique that achieves the highest rate of cure, with a rate of recurrence of less than 5%.[66] A modified Mohs technique is usually used in DFSP, with the tissue fixed in formalin and embedded in paraffin (Figure 11). This modification slows the procedure but allows improved diagnosis of fat invasion by the tumor, which can pass unrecognized in frozen sections.[67]

DFSP is a tumor that rarely generates distant metastases, and when metastasis does occur, it does so only after many years of tumor progression. The rate of metastasis is 1% to 3%, with a mean interval since the first excision of 6 years. As in other sarcomas, metastases preferentially localize to the lung, although they have also been described in the brain, bone, and heart. Although it is difficult to determine which cases are at risk of metastasis, they generally involve recurrent lesions that have progressed for many years and in which a fibrosarcoma component is seen by histology.

In terms of complementary studies for assessment of cases of DFSP, it should be taken into account that lymphatic or hematogenous spread is rare, and therefore, it is only necessary to take a complete clinical history, with assessment of organs and systems, and perform a physical examination including palpation of the lymph nodes. The only diagnostic test that would appear indicated is magnetic resonance imaging of the affected area, since it provides information on the extent of tumor invasion, particularly in cases of frequent recurrence. Computed tomography is not indicated, except in those cases with suspected bone involvement or lung metastases in cases of recurrent or very large DFSP.

New Pharmacological Treatments

The treatment of choice for DFSP is Mohs micrographic surgery or, if unavailable, conventional surgery with wide margins (>3 cm). However, surgical treatment is not always possible. The prognosis of cases with metastasis is very poor, with survival of less than 2 years following detection of metastatic disease and with resistance to conventional chemotherapy. Likewise, patients with DFSP in whom the tumor is locally advanced can not be treated by radical surgery from the outset and prior neoadjuvant treatment is required to reduce the size of the tumor. Chemotherapy and radiation therapy have not proven effective for this, making it necessary to identify new therapies.

Fortunately, since this type of tumor has a characteristic molecular feature—namely the COL1A1-PDGFB fusion protein—that leads to stimulation of tyrosine kinase activity in receptors for PDGF-BB, the use of tyrosine kinase inhibitors extends the opportunity for pharmacological treatment.

Imatinib mesylate (Glivec, Novartis) has been shown to be effective in other tumors (chronic myeloid leukemia, gastrointestinal stromal tumors) by inhibiting tyrosine kinase activity in certain molecular targets (BCR-ABL7, KIT, or PDGFRB). Experiments using cultured DFSP tissue have shown that imatinib interferes with PDGFB. Some authors have proposed that the drug causes apoptosis of tumor cells and that this could completely destroy the tumor, whereas others have suggested that it alters that phenotype of DFSP, reducing its rate of proliferation, and as a consequence, reduces the size of the tumor but does not destroy it completely.

Imatinib has been used successfully in cases of both metastatic DFSP and locally advanced DFSP.[68] It should be taken into account that the COL1A1-PDGFB translocation is present in most but not all cases of DFSP. Currently, imatinib is only available for compassionate use in patients with DFSP who have demonstrated translocation, particularly as a neoadjuvant treatment to reduce the size

of the tumor prior to surgery. Therefore, new possibilities are becoming available for the treatment of DFSP, especially in cases such as local recurrence, distant metastasis, and areas in which complete resection of the tumor due to poor surgical accessibility, or in pediatric cases in which surgery would be mutilating.[62]

Conflicts of Interest

The authors declare no conflicts of interest.

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