Seminars in Diagnostic Pathology (2013) 30, 13-28

ELSEVIER

Seminars in
Diagnostic
Pathology

Dermatofibrosarcoma protuberans: a comprehensive review and update on diagnosis and management

Beatriz Llombart, MD,[a] Carlos Serra-Guillén, MD,[a] Carlos Monteagudo, MD, PhD,[b] José Antonio López Guerrero, PhD,[c] and Onofre Sanmartín, MD[a]

From the [a]Dermatology Department, Instituto Valenciano de Oncología, Valencia, Spain; [b]Pathology Department. Hospital Clínico Universitario de Valencia, Universidad de Valencia, Valencia, Spain; and the [c]Laboratory of Molecular Biology, Instituto Valenciano de Oncología, Valencia, Spain.

KEYWORDS
Dermatofibrosarcoma protuberans;
Fibrosarcomatous;
Imatinib;
Mohs micrographic surgery;
Review;
Genetic

Dermatofibrosarcoma protuberans (DFSP) is a rare superficial tumor characterized by high rates of local recurrence and low risk of metastasis. DFSP occurs most commonly on the trunk and proximal extremities, affects all races, and often develops between the second and fifth decade of life. The tumor grows slowly, typically over years. Histologically, several variants of DFSP have been described and should be well characterized to avoid misdiagnosis with other tumors. These include pigmented (Bednar tumor), myxoid, myoid, granular cell, sclerotic, atrophic DFSP, giant cell fibroblastoma, and DFSP with fibrosarcomatous areas. Of all these variants, only the DFSP with fibrosarcomatous areas is high grade, with a higher rate of local recurrence and distant metastasis. DFSP is genetically characterized by the t(17;22)(q22;q13), resulting in the fusion of alpha chain type 1 of collagen gene and platelet-derived growth factor beta gene. This translocation is present in 90% of DFSP and represents a very useful tool in the differential diagnosis of DFSP with other tumors with similar histology. The standard treatment is wide local excision with at least a 2-cm margin. However, local recurrence after apparently adequate surgical excision is well recognized. Mohs micrographic surgery would be the treatment of choice with a better cure rate and maximal conservation of tissue. When surgery is insufficient, clinical evidence has suggested that imatinib mesylate is a safe and effective treatment in DFSP, especially in cases of local advanced or metastatic disease. This article presents an overview of the state of the art in the clinicopathological management of this disease.

Dermatofibrosarcoma protuberans (DFSP) is a relatively unusual, locally aggressive cutaneous tumor, characterized by high rates of local recurrence, but low risk of metastasis.[1,2] The first descriptions of this entity were made independently in 1890 by Sherwell[3] and Taylor.[4] In 1924, Darier and Ferrand[5] designated this tumor as a progressive and recurrent dermatofibroma. One year later, based on the tendency of the tumor to develop protruding nodules, Hoffman[6] coined the term DFSP. Most early reports of DFSP described the clinical characteristics and the tendency for recurrence after surgical excision.

In 1962, Taylor and Helwig,[7] in a review of 115 cases, described the histologic characteristics of the neoplasia in detail 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. Generally, the neoplastic cells show little or no pleomorphism, and the mitotic rate is low. Histologically, several variants have been described that include pigmented (Bednar tu-

Address reprint requests and correspondence: Beatriz Llombart, MD, Departamento de dermatología, Instituto Valenciano de Oncología, C/Profesor Beltrán Báguena N°8, 46009 Valencia, Spain.
E-mail address: beatriz.llombart@uv.es.

0740-2570/$ -see front matter © 2013 Elsevier Inc. All rights reserved.
doi:10.1053/j.semdp.2012.01.002

mor), myxoid, granular cell, atrophic DFSP, DFSP with fibrosarcomatous areas (DFSP-FS), DFSP with areas of giant cell fibroblastoma (GCF), DFSP/DFSP-FS with foci of myoid/myofibroblastic differentiation, and sclerosing/sclerotic DFSP.

In 1993, immunoreactivity for CD34 in DFSP was described for the first time,[8-10] and continues to be the main immunohistochemical marker for diagnosis of the DFSP, particularly when associated with the absence of immunostaining for factor XIIIa. Nevertheless, 10% of DFSP are negative for CD34, and 25% of DFSP can be positive for factor XIIIa.[11,12]

Cytogenetic analysis of DFSP dates back to 1990, with initial descriptions showing the presence of a recurrent t(17;22)(q22;q13) translocation or of supernumerary ring chromosomes containing material from chromosomal regions 17q22 and 22q13 accompanied by simple chromosome trisomies.[13,14] The combination of fluorescent in situ hybridization (FISH), comparative genomic hybridization, and molecular techniques has been valuable in further deciphering the composition of the DFSP chromosomal rearrangements, showing that these result in the fusion of the alpha chain type 1 of collagen *(COL1A1)* gene with the platelet-derived growth factor beta (*PDGFB*) gene, the transcriptional upregulation of the *PDGFB* gene being the result of this fusion gene.[15-18]

In recent years, a number of advances have been made regarding the immunohistochemical, chromosomal, and molecular features of this tumor. Furthermore, innovative surgical approaches and emerging targeted pharmacologic treatments have piqued new research and clinical interest in DFSP. This article presents a review and update on the epidemiology, histology, immunohistochemistry, cytogenetics, and management of this tumor. Special emphasis will be placed on describing the histology, molecular biology, and the treatment options through Mohs micrographic surgery (MMS) and the use of PDGF receptor inhibitors.

Epidemiology

DFSP is a rare tumor that constitutes <0.1% of all malignancies and 1% of all soft-tissue sarcomas.[1,19] Its incidence in the United States has been calculated to be between 0.8 and 4.5 cases per million individuals per year.[20,21] Nevertheless, DFSP is the most common sarcoma of cutaneous origin.[2]

DFSP most commonly occurs between 20 and 50 years of age, although its can appear at any age. The age spectrum varies from congenital cases to patients >90 years. Although the proportion of pediatric cases in published series of DFSP ranges between 6% and 20%,[7,22] DFSP is an asymptomatic tumor with a slow growth, and we believe, as other authors,[22-25] that many cases diagnosed in adults begin during childhood. In addition, it should be taken into account that GCF is currently considered to be the juvenile form of DFSP.

Although DFSP has been described in all races, it is difficult to draw specific conclusions regarding the racial incidence of DFSP because race is not mentioned in many of the larger series of patients. In a recent epidemiologic study of 2885 cases,[21] the incidence of DFSP in black individuals was observed to be approximately twice that of whites.

The literature reveals an equal sex distribution, with a slight male predominance in some series[21,26,27] and slight female predominance in others.[21,28,29]

DFSP is preferentially located on the trunk. In 40%-50% of cases, the tumor is located in this area, generally on the chest and shoulders; in 30%-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%-15% of cases, DFSP affects the head and neck, generally the scalp, cheek, and supraclavicular area.[1,2] It has been reported that childhood DFSP has a greater tendency toward acral location. Rabinowitz et al[30] reviewed 27 cases of childhood DFSP and found that 14.8% were located on the hands or feet. However, in our review of the 150 pediatric cases of DFSP published till 2006,[23] acral location was reported in <9% of cases. In our experience, acral DFSP is infrequent. We believe that some CD34 positive acral lesions described in the literature as DFSP were in fact other fibroblastic-like lesions, for example, superficial acral fibromyxoma.

A history of trauma as a possible etiologic factor in DFSP has been debated. Such events might favor the development of the tumor, as a history of trauma is reported in 10%-20% of cases.[2, 7] Likewise, cases of DFSP have been described in which tumors are located on the sites of surgical scars,[31] burns,[32] radiodermatitis,[33] vaccination scars,[34] and sites of central venous lines.[35]

Clinical features

The appearance of the tumor depends on the stage of disease, as the tumor progresses slowly over a long period before entering a rapid growth phase.[36] DFSP initially appears as an asymptomatic, indurate plaque that may have a violaceous, red-blue, or brown appearance, with a hard consistency and fixed to the skin but not the deep layers (Figure 1A).[1,7] Over a period, which can vary from a few months to decades, the DFSP grows with the development of multiple nodules within the plaque, from which its name protuberans is derived (Figure 1B and C). Less commonly, DFSP presents initially as a unique firm cutaneous nodule (Figure 1D). In the initial stages of DFSP (Figure 1A), diagnostic errors are common, with the lesion being interpreted as a scar, morphea,[37] morpheaform basal cell carcinoma, atrophoderma, or vascular malformations.[24] When the tumor progresses (Figure 1B and C) or starts as a protruding mass (Figure 1D), DFSP may be confused with another tumor type; however, in our experience, the more frequent mistaken diagnoses are sebaceous cyst, lipoma, or dermatofibroma.