DERMATOFIBROSARCOMA PROTUBERANS

An ESUN Article

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INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a low to intermediate grade soft tissue sarcoma originating from the dermal layer of the skin. Although historically it has been attributed to fibroblastic origin, recent immunohistochemical evidence suggests that it may arise from the dendritic cell in the skin. In 1924, Darier and Ferrand first described the entity of DFSP as a “progressive and recurring dermatofibroma,” underscoring its predilection for local recurrence. DFSP is a locally aggressive tumor and despite sharing some histologic features with fibrohistiocytic tumors, it tends to grow in a more infiltrative manner. Three-dimensional reconstructions of DFSP have shown that the tumor can assume irregular shapes and extend in a villous or finger-like manner. While local recurrence is a common clinical dilemma, metastases are rare and usually occur late in the disease course.

EPIDEMIOLOGY

DFSP comprises roughly .01% of all malignant tumors and approximately 2 to 6 percent of all soft tissue sarcomas. The estimated incidence is 0.8 to 5 cases per 1 million persons per year, which is roughly 1,000 new cases per year in America. The incidence among blacks (6.5 per million) is almost double that among whites (3.9 per million). It most commonly affects patients between 20 and 50 years of age, although it has been described in both children and in the elderly. Congenital DFSP is a recognized entity but is extremely uncommon.

CLINICAL FEATURES

DFSP usually has a long slow indolent course, with early tumors appearing as painless areas of cutaneous thickening (Figure 1). They may have pink, dark red or even bluish discoloration, particularly at its periphery. Over time, they develop into a larger nodular mass, and ultimately can develop into a large fungating lesion (Figure 2). When they grow into the epidermal layer of the skin, they may eventually ulcerate. Unlike tumors of the subcutaneous tissue, DSPF is adherent or intimate with its overlying skin. Typically it is not adherent to underlying structures, with most tumors being superficial and less than 5 cm in size at time of diagnosis.
The duration of tumor growth ranges from months to years and may, in some cases, span decades. DFSP often is mistaken for lipomas, deep-seated epidermal cysts, scars, hypertrophic scars, keloid, dermatofibromas, nodular fasciitis, and insect bites and a delayed diagnosis is not uncommon. The trunk is the most common location (47%), followed by lower extremity (20%), upper extremity (18%), and finally head and neck (14%).

DFSP is a malignant tumor, but only metastasizes 1-4% of the time. Metastasis is a late clinical outcome and typically occurs only after several local recurrences.

**DIAGNOSIS**
Although routine imaging is not necessary, magnetic resonance imaging (MRI) may be helpful to evaluate the local extent of the tumor and may be important in preoperative planning for larger tumors. As with many other soft tissue tumors, T1-weighted images demonstrate low signal characteristics while T2-weighted images exhibit higher signal.

Diagnosis is made using either a core needle or an open incisional biopsy. While the role of fine needle aspiration is established in cases of recurrent disease, initial biopsies should be larger samples that demonstrate the histologic architecture of the tumor.

**Biopsy**
A core needle biopsy (or core biopsy) involves removal of a very small amount of tumor and is performed by inserting a hollow needle through the skin and into the organ or abnormality to be investigated. The needle is then advanced within the cell layers to remove a sample or core. This procedure takes a few minutes to perform and may be undertaken in an outpatient setting.

An incisional biopsy removes only a portion of the tumor for the pathologist to examine. An incisional biopsy is generally reserved for tumors that are larger and offers the pathologist a larger specimen with which to work. This type of biopsy has a slightly higher diagnostic success rate and is usually carried out in the operating room.

An excisional biopsy involves removal of the entire tumor and is typically reserved for very small lesions in which an incisional biopsy or a core needle biopsy is not practical. It is usually performed in cases where removing the entire lesion along with a narrow margin of normal tissue is easily accomplished and tolerated by the patient. This is also often performed in the operating room.

**STAGING**
Although the American Joint Committee on cancer has not set forth a system specific for staging of DFSP, it is currently staged in accordance with the American Musculoskeletal Tumor Society Staging System which takes into account tumor grade and compartmentalization.

**HISTOPATHOLOGY**
DFSP has a characteristic histologic appearance of monomorphous bland spindle cells arranged in a storiform or "herringbone" pattern (Figure 3). Early lesions may demonstrate a "Grenz zone," which is a tumor-free region separating the tumor from the epidermis. Unusual variants of DFSP include the Bednar tumor that is denoted by melanin-containing cells, myxoid DFSP that contains areas of interstitial mucin, and the atrophic type.
Approximately 15% of cases contain a component of high-grade sarcoma. This is frequently, but not exclusively, a fibrosarcoma and therefore is usually referred to as DFSP-FS. The high-grade sarcoma portion can be variable in size, at times encompassing the majority of the underlying DFSP lesion. Even in cases that develop a high grade sarcomatous component, metastatic disease is rare and local recurrence remains the main concern.

Immunohistochemical analysis can be utilized to aid in the diagnosis. Staining for CD34 is commonly employed, and sensitivity has been reported as being between 84 and 100 percent (Figure 4).\textsuperscript{21-23} Positivity for CD34 is lost within the areas of sarcomatous change in cases of DFSP-FS. In addition, staining for hyaluonate is expected to be positive in DFSP, while staining for CD44 is expected to be negative.

**GENETICS**

Most (90%) of DFSP exhibit a characteristic unbalanced chromosomal translocation between chromosomes 17 and 22. The platelet-derived growth factor-B gene (PDGFB; chromosome 22) is fused with the collagen 1 alpha 1 gene (COL1A1; chromosome 17). This t(17; 22) translocation leads to upregulated expression of the fusion oncogene and fully functional PDGFB.\textsuperscript{24-26} The cell then produces a self-stimulatory growth signal, which in turn leads to uncontrolled cell division and a tumor develops.

A **chromosomal translocation** is an abnormal rearrangement of DNA between chromosomes. When the translocation occurs between two nonhomologous chromosomes, it is termed a reciprocal translocation. Reciprocal translocations are usually harmless in carriers; however, there is an increased risk for miscarriages or children with abnormalities. A Robertsonian translocation involves two acrocentric chromosomes that fuse near the centromere region with loss of the short arms. The resulting karyotype leaves only 45 chromosomes since two chromosomes have fused together. Like other translocations, carriers of Robertsonian translocations are phenotypically normal, but there is a risk of unbalanced gametes which lead to miscarriages or abnormal offspring.

**TREATMENT OF DFSP**

The mainstay of treatment of DFSP has been surgery. Because of the high rates of recurrence, historical recommendations have sought 5 cm margins.\textsuperscript{27}
Who treats DFSP?

Dermatologists routinely diagnose and treat lesions of the skin. Most cases of DFSP can be adequately treated by a dermatologist in an outpatient setting. In cases of very large or advanced DFSP, or where major reconstructive surgery will be needed, a multidisciplinary approach is recommended. This involves an oncologist, dermatologist, and a pathologist. In cases involving the deep tissues or bones, the participation of an orthopaedic surgeon specializing in tumor surgery may be necessary. In cases where extensive surgical reconstruction will be necessary, a plastic surgeon may be called upon.

Recent NCCN guidelines recommend margins of 2 to 4 cms using conventional surgical management (Figures 5-7). However, with the advent of Moh’s surgery, complete excision with microscopic margins has yielded excellent outcomes and offers the benefit of decreased surgical morbidity. In a comparative study of wide resection versus Mohs surgery, wide resection was associated with a recurrence rate of 13% whereas Mohs surgery had no recurrences at 5 years.28

The Surgical Procedure

Mohs surgery, created by Dr. Fredrick E. Mohs, is microscopically controlled surgery that is highly effective for common types of skin cancer. The surgery involves four steps:

1. Surgical removal of tissue.
2. Mapping the piece of tissue, freezing and cutting the tissue and staining with H&E or other stains.
3. Interpretation of microscope slides.
4. Reconstruction of the surgical defect.

The procedure is usually performed in a physician's office under local anesthetic. A small scalpel is utilized to cut around the visible tumor. A very small surgical margin is utilized, usually with 1 to 1.5 mm of "free margin" or uninvolved skin. Because the Mohs procedure is microscopically controlled, it provides precise removal of tumor, while healthy tissue is spared.
Imatinib mesylate was designed as an abl-kinase inhibitor to treat Philadelphia chromosome positive leukemia (chronic myelogenous leukemia). The application of imatinib to DFSP has been limited but encouraging. In one series, 10 patients with either locally advanced or metastatic disease showed variable response to imatinib treatment. Of note was the association shown in one patient between the lack of the t(17,22) translocation and the lack of response to imatinib treatment. Additional reports of successful use in cases of metastatic or surgically unresectable DFSP have been published. A woman with recurrent DFSP of the upper back and metastasis to the axilla and lung responded well following one month of treatment. At 3 months, the tumor regressed markedly and computed tomography imaging showed near complete resolution of the lung metastasis. A man with DFSP of the thigh and metastatic disease of the spine was treated with imatinib for 4 months and shown to have a 75% reduction in tumor size, permitting surgical resection. The resected tumor showed no signs of malignancy, demonstrating a full histopathologic response to treatment. Imatinib is approved for the treatment of adult patients with unresectable, recurrent, or metastatic DFSP who are not eligible for surgery.

The effectiveness of Imatinib in the treatment of DFSP is likely related to the tumor’s dependence on this pathway with the common translocation driving the constitutive expression of the PDGF ligand. This is a unique example of a tumor that responds to a specific targeted therapy which is not based on genetic amplification or mutation. The limitation on developing imatinib clinically for the treatment of DFSP is that it is a benign to intermediate grade tumor in which complete surgical resection obviates the need for systemic therapy. Imatinib likely will be only applicable to the subset of patients with unresectable, recurrent or metastatic disease. That said, Phase II trials of treating DFSP with imatinib are currently in progress.

Numerous studies have investigated the use of radiotherapy in the treatment of DFSP. Currently, there is limited objective data to support its routine use; however, successful application has been reported in a few small series. In one study, 10 patients with DFSP (one of which was DFSP-FS) were treated with surgery and post-operative radiotherapy. At the time of latest follow-up (21-185 months) nine of the patients remained free from recurrence. The patient with DFSP-FS experienced a local recurrence and eventually died with disease. In other reviews, it was concluded that DFSP is radiosensitive and adjuvant radiotherapy may be considered in patients where repeated surgery may cause mutilation or functional impairment.

PROGNOSIS

The general prognosis for DFSP is excellent. The overall rate of distant metastasis is only 5% and regional metastasis is 1%. Historically, recurrence rates have been high, ranging from 11%-53%, but with the advent of Mohs surgery, the rates have dropped. Even with recurrent DFSP, Mohs surgery has a 98% cure rate. Metastasis is associated with a poor prognosis, with few patients surviving past two years. With initial encouraging results using imatinib, improved prognosis even in cases of metastatic disease may be realized.

REFERENCES


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