

Dermatofibroma Protuberans Arising From an Infected Insect Bite

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Case Report

A 47-year-old female was admitted with a painful, fungating left buttock mass, enlarging rapidly over the prior 2 months, associated with an unintentional 20-pound weight loss. She stated that it started as an insect bite that never resolved; medical attention was not sought previously since she was homeless at that time. The patient denied fever, chills, bone pain, or any other constitutional symptoms. Family history and past medical history were unremarkable. Social history revealed that she had been homeless for some time with limited access to food and shelter; otherwise negative for tobacco, alcohol, or illicit drugs. On physical exam, the patient was not cachectic, and there was no palpable lymphadenopathy. Respiratory, cardiovascular, and gastrointestinal exam was within normal limits. Skin examination revealed a purulent, fungating, malodorous 20 cm x 15 cm pink exophytic mass on the left supragluteal region (Figure 1). Blood cultures and HIV screen were negative. Magnetic resonance imaging (MRI) showed a large enhancing soft tissue mass within the left gluteal region, with no evidence of extension into underlying musculoskeletal structures. Positron emission tomography/computed tomography (PET-CT) scan showed a large irregular left gluteal area of hypermetabolic activity corresponding to a large soft tissue mass on the CT portion of the exam, and a focal hypermetabolic gastrosplenic lymph node concerning for malignancy (Figure 2). Histologic examination of tissue biopsy showed densely infiltrative spindle cells arranged in a storiform pattern, suggestive of a tumor of mesenchymal origin, with no obvious evidence of high-grade features such as mitosis or anaplasia. Immunohistochemical stains

were positive for CD34, vimentin, and bcl-2 (weakly positive), and negative for CD31, S100, pancytokeratin, desmin, HMB45, and SMA, consistent with dermatofibrosarcoma protuberans (DFSP). The patient was seen by radiation oncology and preoperative radiotherapy was planned; it was to be followed by definitive surgical resection. Laparoscopic biopsy of the gastrosplenic lymph node to evaluate for oligometastatic disease is planned.

Discussion

DFSP is a rare intermediate- to low-grade sarcoma with an incidence of 0.8–5 cases per million per year.¹ It was initially described in 1924 by French pathologists Darier and Ferrand,² and given its present name in 1925 by Hoffman. Usually presenting as an indolent violaceous lesion in the trunk or proximal extremities, it is rarely found above the neck, and is more common in the 20–50 year age group. These lesions may remain indolent for years before enlarging and ulcerating due to rapid growth and expansion of overlying skin. The lesion is typically mobile on subcutaneous structures and expands by infiltrating bordering skin and subdermal structures. It is typically asymptomatic in the early stages, although some patients may complain of pruritus and local discomfort. The causative event is unknown, but 10–20% of patients report prior trauma, vaccinations, burns, or surgical incisions at the lesion site. DFSP is considered a locally aggressive disease with local recurrence rates as high as 60% in some studies.³ Metastatic potential is low, with 1% local and 4–5% distant metastasis, usually via hematogenous spread to the lungs. Tissue biopsy is required for diagnosis, and histologic examination reveals an abundance of spindle cells arranged in a storiform or cartwheel pattern in a bed of collagen, as well as fingerlike projections extending into the dermis.³ Many tumors show a pseudo-border of connective tissue on the periphery and can be erroneously determined to be encapsulated. Tumors in

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Figure 1. Left buttock fungating mass, 20 cm x 15 cm.

which the typical storiform histologic pattern is replaced by a frond-like herringbone arrangement of cells with increased mitotic activity show a greater propensity for local recurrence and eventual metastasis. Rare variants of DFSP include a hyperpigmented form due to scattered melanin-containing cells, known as a Bednar tumor, seen in roughly 5% of cases and a myxoid-predominant type. Immunostaining for CD34(+) or factor XIIIa(-) differentiates DFSP from dermatofibromas and fibrosarcomas,⁵ and CD34 staining is also used to identify post-resection margins. On cytogenetic analysis, the collagen type 1 A1 (COL1A1) gene on chromosome 17 is fused to the platelet-derived growth factor β (PDGF- β) gene on chromosome 22. This reciprocal t(17;22) translocation results in constitutive overexpression of PDGF- β , which then activates tyrosine kinase receptors on the tumor cells causing uncontrolled proliferation of fibroblasts.⁴ There is no formal American Joint Committee on Cancer staging for DFSP, so this is simplified as follows: stage 1 (local disease), stage 2 (regional disease), and stage 3 (distant disease). The primary treatment modality is surgical resection with 3–5 mm margins, but tendency for irregular borders and finger-like projections makes clear margins difficult, and histologic review is mandatory. Overall prognosis is directly related to the extent of resection, with a reported 11–20% recurrence rate using traditional surgical approaches. Moh's microsurgery has shown impressive results, facilitating challenging cosmetic reconstructions and presenting with local recurrence rates between 0 and 6%.⁶ Adjuvant radiation is recommended, especially when adequate resection margins are questionable or impractical due to the size and anatomical limitations. Usually, a 5,000–6,000 cGy dose is indicated for close or positive margins, although this may also be done preoperatively. This carries a small but definite risk of transforming some DFSPs into aggres-



Figure 2. Positron emission tomography/computed tomography scan showing hypermetabolic left gluteal mass.

sive sarcomas, thus close follow-up is required. Tyrosine kinase inhibitor imatinib (Gleevec, Novartis) was approved by the U.S. Food and Drug Administration on October 19, 2006 for use in unresectable, recurrent, or metastatic disease demonstrated to have t(17;22) by cytogenetic analysis (90% of tumors). The mechanism of action is based on inhibition of PDGF- β mediated tyrosine kinase activation and a treatment dose of 800 mg/day.⁷ The initial open label multi-center phase II study showed an 83% overall response rate in treated patients, with 39% of patients achieving complete response and 44% partial response. Median duration was 6.2 months (range, 4 weeks–20 months).⁸ Several other studies by the Sarcoma Alliance for Research through Collaboration (SARC) are currently evaluating the role of imatinib in a neoadjuvant setting.

Most recurrences will occur within the first 3 years, and 25% occur within 5 years. In a large Memorial Sloan-Kettering Cancer Center case review from a series of 159 patients, median time to local recurrence was 32 months. Distant metastatic disease risk increases with the number of local recurrences. Post-treatment surveillance with thorough clinical exams every 3–12 months for the first 3 years and yearly thereafter is suggested

in current guidelines. Careful attention, and biopsy of any suspicious lesions, especially on excision site, and complete skin examination is required. Further investigations in the absence of clinical suspicion of metastatic disease are not indicated.

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Review

Dermatofibrosarcoma Protuberans: Histologic Approach and Updated Treatment Recommendations

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Dermatofibrosarcoma protuberans (DFSP) is a rare low-grade sarcoma that often comes to the attention of dermatologists and dermatopathologists due to its relatively superficial location and easy access to biopsy. The report by Zaiden and colleagues illustrates an unusual advanced case with a striking clinical presentation.¹ The patient presented with a large fungating mass on the left supragluteal region, limited to the soft tissue by magnetic resonance imaging (MRI) studies, without extension into the underlying musculoskeletal structures. The lesion was easily assessed by performing a skin biopsy, which showed the characteristic features of DFSP. The histology demonstrated a proliferation of spindled cells that were arranged in a storiform pattern. The lesional cells were strongly

positive for CD34. The histologic differential diagnosis for this process, as well as the implications of making this diagnosis, will be reviewed.

Brief Overview of Clinical Features

DFSP is a tumor of young individuals with presentation often limited to the trunk, with less common presentations on the head and neck and proximal portions of the extremities. It is extremely rare on the hands and feet, and therefore, easy to distinguish from histologically similar lesions that do occur on the digits.² The tumors are slow growing and can reach an enormous size over a number of years. They are hardly ever under the size of 2 cm, and often range in size from 4–5 cm.

Differential Diagnosis of Cutaneous Spindle Cell Lesions

The presence of a spindle cell proliferation within the skin raises a differential diagnosis that includes invasive spindle cell squamous cell carcinoma, spindle cell melanoma, neural tumors (ie, malignant peripheral nerve sheath tumor), smooth muscle tumors (ie, leiomyosarcoma), and angiosarcoma (least likely). The characteristic features of DFSP include a dense proliferation of spindled cells that is significantly based in the subcutis. The lesion overall is not well circumscribed. The lesional cells extend significantly into the dermis and are thus sampled by superficial skin biopsies. Unfortunately, superficial biopsies miss the characteristic histologic features of DFSP. These include extension of the lesional cells into the fat with encircling of individual adipocytes (so called “string of pearls” pattern) and/or encircling of entire fat lobules (so-called

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“honeycomb” pattern).³ On high power examination, one does not usually see cytologic atypia or significant mitotic activity. The cells typically demonstrate a storiform or cartwheel arrangement, which is quite characteristic of this disorder.

The presence of strong CD34 staining in this histologic context is diagnostic of DFSP. The lack of staining with cytokeratins argues against a carcinoma. Likewise, negativity for S100 and HMB45 argues against neural and melanocytic origin, respectively. The lack of staining with smooth muscle actin (SMA) and desmin excludes leiomyosarcoma and the lack of staining with CD31 in this context excludes angiosarcoma.

One often considers variants of dermal fibrous histiocytomas in the differential diagnosis of DFSP. This can be a particular problem in fibrous histiocytomas that are cellular and extend deep into the subcutaneous tissue and entrap fat, a key feature of DFSP. These can sometimes be focally positive for CD34. The important histologic findings that distinguish fibrous histiocytomas from DFSP include the presence of foam cells, giant cells, and inflammatory cells in fibrous histiocytomas, as well as more ovoid cells and increased mitotic activity. The cells of DFSP tend to be uniform and monomorphic with small, slender nuclei and mildly eosinophilic to amphophilic cytoplasm. There are very few, if any, mitotic figures. Moreover, fibrous histiocytomas often contain epidermal changes, such as acanthosis and follicular differentiation, unlike DFSP, which usually has a normal to slightly thinned epidermis. Most fibrous histiocytomas are only focally positive for CD34 and express many more CD163+ histiocytes than DFSP.⁴ The exception to this rule is the newly described deep “benign” fibrous histiocytoma, a lesion usually based in the subcutis which is also CD34 positive in approximately 40% of cases.⁵ The other morphologic features of fibrous histiocytomas are preserved, however, and can be used to differentiate from DFSP. These include the presence of lymphocytes and other inflammatory cells; the plump, ovoid nature of the lesional cells; and the lack of characteristic infiltration of the fat that is usually seen in DFSP.

Important Variants of DFSP

While most cases of DFSP are cellular, there are variants in which the cellularity is decreased, and these areas can co-exist with areas of more conventional DFSP.⁶ These lesions have been termed the myxoid variant of DFSP. They are often paucicellular with an edematous to mucinous stroma and an arborizing vascular pattern. They can pose diagnostic difficulty unless, as stated, more conventional areas of DFSP exist, or can be seen in a recurrence of the lesion.

Pigmented DFSP (so called Bednar tumors) show histologic features similar to conventional DFSP, except that they are admixed with numerous dermal dendritic melanocytes and melanophages.⁷ The pigmented cells are S-100 positive and in small biopsies, the lesions may be mistaken for melanoma. The nonpigmented tumor cells, however, are S-100 negative and CD34 positive. Recently, we described a variant lesion that showed overlapping features between pigmented dermatofibromas and Bednar tumors.⁸ These lesions may well represent an early version of Bednar tumors, although they appeared to have an unremarkable clinical course on limited clinical follow-up.

Giant cell fibroblastoma is a tumor of children that also occurs on the trunk, similar to DFSP.⁹ The tumor is characterized by spindled bland fibroblasts and stellate cells admixed with giant cells, and the latter often line irregular, ectatic vascular spaces (so called “angiectoid spaces”). The stroma is often paucicellular, and vascular spaces are numerous. These lesions can co-exist with areas of DFSP, and indeed, DFSP can recur as giant cell fibroblastoma, and giant cell fibroblastoma can recur as DFSP. Both contain CD34+ lesional cells and the characteristic COL1A1-PDGFRB ring or linear translocation [t(17:22)], prompting most observers to regard them as related tumors.^{10,11}

Fibrosarcomatous Transformation and Treatment Considerations

While DFSP is generally regarded as a low-grade sarcoma with a potential for locally aggressive clinical behavior, its metastatic potential is considered to be low.⁹ Cases with fibrosarcomatous areas, however, continue to be problematic with respect to predicting metastatic behavior. Fibrosarcomatous areas are characterized by more highly cellular areas, with spindle shaped cells arranged in a “herring bone” pattern, often accompanied by increased mitotic activity. The transition between the 2 areas is either abrupt or gradual. The areas of conventional DFSP are strongly CD34 positive, whereas the areas of fibrosarcomatous transition often show loss of staining. In one study of 41 cases, metastases were seen in 14% of cases, and 2 patients died of disease.¹² No morphologic features were found to be predictive of outcome. Similar results were found in a second series of 9 patients.¹³ In contrast, a second study of 18 patients with fibrosarcomatous change in DFSP found that none showed metastases or disease-related deaths, provided that complete excisions were performed.¹⁴ Nevertheless, fibrosarcomatous change within DFSP is considered a finding of concern, and these patients should undergo complete excisions with close clinical follow-up to monitor for the development of metastatic disease.

Excision of DFSP Using Mohs Micrographic Surgery

Mohs micrographic surgery, a skin sparing procedure often used to treat other types of skin cancer, has only recently been extensively used in the treatment of DFSP. A recent study comparing the outcome of 79 patients who were treated with either wide local excision or Mohs surgery found that none of the patients treated with Mohs surgery experienced local recurrences, whereas 5 of those with wide local excisions did.¹⁵ In addition, as there can be significant morphologic overlap between scar formation and DFSP, immunohistochemical stains for CD34 on paraffin embedded tissues are often used in conjunction with Mohs surgery to evaluate margins.¹⁶ This results in a better outcome for the patient overall.

Conclusion

The case presented by Zaiden and colleagues illustrates a relatively dramatic but typical presentation of this rare and unusual cutaneous tumor. It discussed many of the pertinent clinical, histologic, and treatment considerations for this tumor. Important considerations in the workup of this tumor included CT scanning to determine the extent of involvement, assessment for the presence of fibrosarcomatous transformation, and perhaps consideration for newer treatment modalities such as the use of Mohs micrographic surgery and imatinib.

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