

## CLINICAL VIGNETTE

# Dermatofibrosarcoma protuberans

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### Case Report

A 33-year-old previously healthy Asian male presented with a right lower neck mass. He initially noticed a painless lump in his right supraclavicular area about one year prior. It was initially described as a soft, rubbery, movable lump under the skin. He denied fever, chills, weight loss, night sweats or other constitutional symptoms. Because the lump was gradually increasing in size, he sought medical attention. On initial physical examination, there was a 2 x 3 cm smooth firm mass at the right supraclavicular area not adherent to the skin. There were no other palpable lesions nor organomegaly on examination. He underwent an excisional biopsy of the mass. Microscopic pathology revealed a “low-grade malignant spindle cell mesenchymal neoplasm, morphologically most compatible with dermatofibrosarcoma protuberans (DFSP).” However, it was noted that the immunoprofile was not entirely characteristic of DFSP because CD34 was negative, and 90% of DFSPs are positive for CD34. A note was also made that lesion was associated with local infiltration into adjacent adipose tissue and skeletal muscle. The patient was referred to medical oncology for recommendations regarding the management of his malignancy.

### Discussion

Dermatofibrosarcoma protuberans (DFSP) is a rare, infiltrative cutaneous soft tissue sarcoma. Based on the SEER (Surveillance, Epidemiology, and End Results) data from 1992 to 2004, the estimated overall incidence of DFSP in the United States ranges from 2.7 to 6.4 per 1,000,000 person-years.<sup>1,2</sup> It is the second most common type of cutaneous soft tissue sarcoma, second only to Kaposi sarcoma.<sup>1</sup> It is usually locally aggressive and associated with distant metastases. The local recurrence rate for DFSP ranges from 10% to 60%. Development of regional or distant metastasis is significantly lower at 1% and 4% to 5%, respectively.<sup>3-5</sup> Regional lymph node metastasis is rare, and in cases of distant metastasis, the lungs are the most common site.

Patients usually present with an indolent, asymptomatic skin lesion that gradually enlarges over a period of months to years. As the skin lesion grows larger, it may become painful and even ulcerate. A dermatologist or a surgeon is usually involved early in the care of the patient, and an adequate biopsy is needed for the diagnosis of DFSP. Accurate pathological diagnosis requires careful review of the tumor tissue by an experienced sarcoma pathologist. This tumor is frequently misdiagnosed due to inadequate tumor tissue sampling. Therefore, incisional biopsy or deep punch biopsy is strongly recommended for an

accurate diagnosis. Histologically, DFSP cells are typically spindle cells with low mitotic rates arranged in a storiform pattern and are usually bland with minimal cytologic atypia.<sup>5</sup> There may be peripheral tumor extensions invading surrounding tissues. Because these invading cells may have a bland appearance, it can be difficult for the pathologist to determine tumor resection margin status. Immunohistochemistry (IHC) is used to differentiate DFSP from other subtypes of soft tissue sarcomas. DFSP is usually CD34 positive, hyaluronate strongly positive, factor XIIIa negative, SMA negative and S-100 negative.<sup>6,7</sup> IHC can also be useful in supplementing H&E specimen review by light microscopy in determining margin control from surgical resection. At the molecular level, over 90% of DFSP tumors have an unbalanced translocation t(17;22)(q22;q13) that creates a fusion gene in which a growth factor gene, *PDGFB*, is fused with a highly active *COL1A1* gene. The resulting PDGFB/COL1A1 fusion protein then results in unregulated expression of tyrosine kinase PDGFRb which leads to cell proliferation and tumor growth. Because of this unique molecular finding, molecular studies including RT-PCR or FISH for the oncogenic chimeric fusion gene can be very useful for the pathologist when the DFSP diagnosis is in doubt.<sup>8,9</sup> There is also an aggressive subtype of DFSP called fibrosarcomatous DFSP (FS-DFSP). In contrast to conventional DFSP, FS-DFSP is associated with a high-grade sarcomatous component with cytologic atypia and higher mitotic rates (>5/10 HFP) admixed with other morphologically typical DFSP cells.<sup>5</sup> CD34 expression is usually absent in FS-DFSP sarcomatous cells. FS-DFSP tumors have a higher rate of metastases and overall poorer prognosis.<sup>10,11</sup>

Staging evaluation for DFSP includes a thorough physical exam. A full skin and regional lymph node exam are necessary. Imaging of the tumor site can be done for treatment planning by providing information on the depth of invasion. MRI with intravenous contrast is the preferred imaging modality over CT scan unless there is a concern for underlying bone involvement. Since distant metastatic disease is rare, additional imaging study is usually reserved for recurrent tumors, FS-DFSP, and patients with high clinical suspicion for metastatic disease.

Treatment of choice is complete surgical resection with negative margins for localized DFSP. Lymph node evaluation is not required for patients without clinical evidence of lymphadenopathy. Because of its high rate of local recurrence, guidelines from the National Comprehensive Cancer Network (NCCN) recommend a margin of at least 2 cm if a wide local excision is

performed.<sup>5</sup> Mohs micrographic surgery is also a viable alternative to wide local excision (WLE). Studies have shown that Mohs surgery can lead to lower local recurrence rate when compared to WLE.<sup>12</sup> If a positive margin is noted on the surgical specimen, repeat resection is indicated to establish clear margins unless further surgery is not anatomically feasible. In general, for locally recurrent disease, surgery remains the preferred treatment of choice. DFSP is a radiosensitive neoplastic disease, but definitive primary radiation therapy (RT) alone is not the preferred therapeutic modality. Radiation therapy is currently indicated in patients with a positive surgical margin if no further surgical intervention is feasible. Dosage up to 50 to 60 Gray (Gy) for indeterminate or positive margins is recommended, and the fields of radiation typically extend 3 to 5 cm beyond the surgical margin.<sup>5,13</sup> A study of 53 patients showed that combined surgery and radiation therapy achieved local control rate and disease-free survival of 93% at ten years.<sup>14</sup> RT is also an option for recurrent DFSP if it has not been previously administered.

DFSP is characterized by a unique chromosomal aberration with important therapeutic applications. The translocation involving long arms of chromosomes 17 and 22, t(17;22)(q22;q13), results in high overexpression of PDGFRB receptor. This singular biological feature has allowed for the use of small molecule tyrosine kinase inhibitors (TKI) to be used in the management of DFSP, since TKIs exhibit high-affinity binding to PDGFRB receptor. In particular, imatinib mesylate is currently FDA approved for the treatment of advanced, metastatic DFSP. In this setting, two phase II studies showed overall response rates approaching 50% with median time to progression of 1.7 years.<sup>15</sup> Adverse effects were similar to those commonly seen with imatinib mesylate. Namely, cytopenias, fatigue, peripheral edema, and skin rash. In addition, sustained complete remission of metastatic DFSP with the use of imatinib mesylate has been reported.<sup>16</sup> Furthermore, because of its high degree of activity in the metastatic setting, imatinib has also been used in the neoadjuvant and adjuvant setting. A multicenter phase II clinical trial of 14 patients examined daily use of neoadjuvant imatinib and found it effective and well tolerated.<sup>17</sup> This clinical trial is overall response rate after twelve weeks of treatment was 57%, including one unconfirmed complete response.

For cases of metastatic disease refractory to imatinib therapy, the therapeutic options are currently limited. Nonetheless, some studies have shown considerable activity for other available TKIs. One study assessed the activity of sunitinib in a cohort of thirty patients refractory to imatinib therapy. Daily, oral Sunitinib was administered for four weeks on and two weeks off, or was continuous lower daily dosing. The overall disease control rate was 80% including two complete responses. Median progression free survival and overall survival were 19 and 27 months respectively.<sup>18</sup> Conventional chemotherapy regimens such as AI (doxorubicin, ifosfamide), low dose methotrexate, and vinblastine can also be considered. Unfortunately, there is generally a lack of clinically significant responses of metastatic DFSP to conventional cytotoxic chemotherapy agents. In some cases, palliative repeat resection, radiation therapy or clinical trials should be considered under these circumstances.

Upon completion of definitive treatment for DFSP, lifelong active surveillance is essential because late DFSP recurrences are not uncommon after initial surgery. NCCN recommends that the primary site be examined every 6 to 12 months, and all patients should be educated about regular, detailed self-examination of the scar site.<sup>5</sup> Patients should also be educated on the signs and symptoms of metastatic disease. For carefully selected patients, surgical resection of isolated recurrent metastatic disease can result in long-term disease control and potentially be curative.

### *Clinical Case Follow-up*

At the time of initial medical oncology consultation, the patient did not have any signs or symptoms to suggest metastatic disease. He also did not have any gross disease at the site of his surgical scar, and clinical lymph node examination was normal. Molecular studies using FISH technique to assess for amplification of *PDGFB* gene locus on 22q13 was requested since the tumor was uncharacteristically CD34 negative. Molecular profiling revealed positive results supporting the final diagnosis of dermatofibrosarcoma protuberans (DFSP). Because the surgical margin was positive on initial excisional biopsy, the patient was referred to head and neck surgeon for repeat surgical excision.

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Submitted August 14, 2018