

# **Dermatofibrosarcoma protuberans: A case report and literature review**

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**ABSTRACT:** Dermatofibrosarcoma protuberans is a rare malignancy comprising approximately one percent of all sarcomas and approximately less than 0.1% of malignancies. Although rarely metastatic, significant tissue loss and deformity can occur with wide local excision. The mass tends to be slow growing and disregarded until significant growth or skin changes occur. Recent advances in molecular diagnostics have led to the discovery of a translocation of COL1A1 and PDGFR $\beta$  (17q22;22q13) and thusly the implementation of treatment with Imatinib mesylate (GLEEVEC<sup>TM</sup>). In several small case series and phase II trials, imatinib has shown promise with recurrent and unresectable disease. Radiotherapy is useful in cases with microscopically positive margins to achieve local control.

**CASE PRESENTATION:** A 44 year old male presented for evaluation of two discrete chest wall masses. The first, more superior mass, was located directly above the sternum at the level of the fourth rib, had been present for approximately five years, slow growing, painless and 2 cm in diameter. The second, was located inferiorly and immediately to the right of the xiphoid, also painless and approximately 1.5cm in size. The second mass had only been present for approximately one year after sustaining chest wall trauma. The mass had been growing steadily for six months prior to evaluation. Past medical history was significant for controlled hypertension on an ACE inhibitor. Past surgical history was significant for removal of a benign lipoma from his left axilla in January 2013. The patient described these masses to be the same as that within the axilla. Due to the considerable growth of the inferiorly located mass, the patient had sought excision. Prior examinations did not mention the mass within the examinations.

On exam, this healthy-appearing male appeared younger than his stated age. The left axillary scar was well healed. Two chest wall masses were appreciable on visual inspection alone. The masses were firm, mobile within the subcutaneous tissues and without overlying skin changes or tenderness. No appreciable communication between the two masses was found on palpation.

Due to the history of chest wall trauma, a CT scan with intravenous contrast was ordered to further elicit the nature of these masses. The imaging (shown below) revealed two distinct, non-encapsulated masses. No gross invasion was present into the surrounding tissues. The masses were isodense with nearby musculature. The superior mass was 42 Hounsfield units and the inferior ranging from 18 to 24.

The patient was taken for excision of these masses under local anesthesia. Intraoperatively, longitudinal incisions were made immediately over the masses. The superior mass was able to be removed in one complete piece. The inferior mass was removed in piecemeal sections due to its friability. Both masses appeared lipomatous, rubbery and smooth-textured

without gross calcification. The tumor beds displayed an unusual amount of capillary bleeding after removal and extensive electrocautery was required in addition to digital pressure to achieve hemostasis prior to closure.

Post operative follow up revealed well healing incisions at the former sites of the masses. The patient had no complaints and residual pain was controlled with over the counter NSAIDs. Pathology reported that both masses consisted of sheets of spindle cells with mitotic figures in a storiform pattern infiltrating into the subcutaneous fat (image shown below). Staining revealed that these masses were vimentin and CD 34 positive. (CD 31, CD 117, S100, SMA negative) Surgical margins contained tumor cells. The diagnosis of dermatofibrosarcoma protuberans was made. Plastic surgery consultation was requested, and the patient was scheduled for excision of remaining tumor. Wide local excision with intraoperative frozen section examination of margins was performed by the initial surgeon with closure and skin grafting performed by the plastic surgery group. Permanent pathology revealed negative margins.

**DISCUSSION:** Dermatofibrosarcoma protuberans (DFSP) is a rare tumor comprising approximately one percent of all sarcomas and less than 0.1% of all malignancies yearly.<sup>13</sup> However, this is the most common sarcomatous lesion encountered within the skin.<sup>7</sup> Annual incidence is between three and five persons affected per million annually. The first documented case was described by Taylor in 1890. The clinical histopathological entity was described in 1924 by Darrier and Fernand with the name proposed by Hoffman in 1925.<sup>11,17</sup> In 1962, the first large series on this tumor was published from data procured from the United States Air Force. This study offered evidence that 17% of patients diagnosed with DFSP had a history of trauma to the area. Latency periods from the time of injury to noticeable growth ranged from 3 weeks to 30 years. This paper also established diagnostic criteria, i.e. the storiform pattern of spindle cells, which describes the typical microscopic pattern to diagnose DFSP. This paper also notes the high rate of recurrence of 30 to 60%, a statistic which still persists.<sup>16</sup> Surgical resection is the undebated mainstay of treatment, with tumor margins recommended at 1.5cm for tumors less than 2cm and margins of 2.5cm to achieve clearance for tumors larger than 2cm.<sup>15</sup> Radiation and chemotherapy are typically reserved for those patients with positive margins or local recurrences.<sup>17</sup>

The differential diagnosis of these tumors includes keloid, epidermal inclusion cyst, hypertrophic scar, malignant melanoma, metastatic carcinoma, dermatofibroma, Bednar tumor, and a fibrosarcomatous malignant transformation of the DFSP.<sup>5,15, 17</sup> While DFSP displays a storiform pattern, DFSP-FS displays a herringbone pattern of the cells. The benign differential when seeing cells of this quality is Dermatofibroma. DFSP clinically are firm, solitary nodules that arise most frequently on the trunk. They often develop as discreet aggregated protuberant masses without a capsule or plaque that may ulcerate. Microscopically they show a honeycomb pattern growing into the surrounding tissues.<sup>5</sup> They may be pink, yellow, or skin color plaques which grow to be multilobulated. The trunk is the most common location affected, with 42 to 72% of cases, the extremities with 16 to 30%, and the head and neck regions with 10 to 16%. While metastases occur in approximately 5% of DFSP, a metastatic rate of at least 15% is seen in DFSP-FS. The lungs appear to be the most commonly affected site of metastases but the pelvis, brain, spinal cord and liver have been reported.<sup>7</sup> Local recurrence is common, occurring in as many as 60%.<sup>16</sup> However, the fibrosarcomatous variant has recurrence rates ranging from 75 to 90%.<sup>11</sup> Overall prognosis is generally good after surgical excision however increased patient age, high mitotic index, increased cellularity are predictors of poor clinical outcomes.<sup>2</sup>

Pathologically, these malignancies are defined by the translocation of chromosomes 17q22 and 22q13 that code for the genes for Platelet Derived Growth Factor Receptor beta (PDGFR $\beta$ ) and collagen type Ia1 (COL1A1). The continuous upregulation of PDGFR $\beta$  causes

an autocrine and paracrine loop increasing the growth of the tumor as a consequence of the propagation of the mitotic signal.<sup>13</sup> This rearrangement could transform NIH3T3 cells suggesting that this translocation is the primary inciting event of DFSP.<sup>4</sup> With further dedifferentiation to the fibrosarcomatous variant of dermatofibrosarcoma protuberans (DFSP-FS), the copy numbers are increased.<sup>13</sup> Most cases of DFSP do not rely in the diagnosis being made with Fluorescent *in situ* hybridization, although in cases of atypical or metastatic disease, the COL1A1-PDGFR $\beta$  marker is a useful tool in making the diagnosis.<sup>12</sup>

Immunohistochemical staining further delineates the differences in these tumors with dermatofibromas being negative for the CD34 receptor and the malignancies being positive.<sup>18</sup> Vimentin a marker of mesenchymal origin is found in all cases. CD117 is negative in all cases of Dermatofibroma and DFSP as CD117 is expressed in gastrointestinal tumors.<sup>3,7</sup> Apolipoprotein-D (Apo-D) has also been described as a tumor marker, found to have worse prognosis when absent, much like CD34.<sup>10</sup>

Targeted therapy serves as the most significant advance in the treatment of DFSP and its fibrosarcomatous variant. Imatinib mesylate, also known as Gleevec, is a tyrosine kinase inhibitor that competes with the adenosine triphosphate (ATP) molecule. This inhibits the aberrant signal transduction and partially restores proper signal transduction.<sup>12</sup> Imatinib has been hailed for its treatment of GIST (gastrointestinal stromal tumors) due to its actions on KIT, PDGFR $\beta$ , PDGFR $\alpha$ , and *acl-bcr*.<sup>1</sup> In 2006, the FDA approved the use of Imatinib for the treatment of DFSP in adults. It has not been approved for treatment in pediatric populations, although 35 cases have been reported congenitally and 160 in the pediatric population.<sup>7</sup> The use of imatinib has been widened to neoadjuvant therapy allowing the tumor to be reduced in size that wide local resection can be performed on tumors which would otherwise lead to significant loss of function due to location prior to therapy.<sup>13</sup> Wicherts reported the case of a 47 year old male with locally recurrent DFSP of the right clavicular region which had been treated with wide local resection twice. Due to its location the tumor would cause significant disability if resected. After six months of imatinib therapy, 400mg daily, the tumor was able to be resected while preserving vital structures.<sup>18</sup>

The first large scale clinical trial with Imatinib was described in 2005 by McArthur. Twelve patients with advanced disease received imatinib 400mg twice daily with 83% response rate. 50% had partial response and 33% had complete clinical remission.<sup>8</sup> More recent studies have had several small case series and case studies on patients with unresectable and recurrent DFSP and DFSP-FS. The European Organization for Research and Treatment of Cancer (EORTC) and Southwest Oncology Group (SWOG) had combined 25 patients with locally advanced or metastatic tumors. Of these, 12 had progression at follow up. The one year progression-free rate was 57%, with progression-free survival of approximately 50% at three years and overall survival of 70% at four years.<sup>13</sup>

In July 2013, Hong et al described the case of a 43 year old female with a tumor resistant to imatinib therapy. The patient had received 400mg daily for three months with disease progression, the dosing was accordingly increased to 800mg daily with further growth of the tumor. Comparison of the initial tumor with the distant recurrence showed that both possessed the COL1A1- PDGFR $\beta$  fusion gene. However, whole genome sequencing revealed that the resistant tumor possessed mutations in *ACAP2*, *CARD10*, *KIAA0556*, *PAQR7*, *PPP1R39*, *SAFB2*, *STARD9*, *ZFYVE*.<sup>6</sup> *CARD10* is associated with the activation in the NF- $\kappa$ B signal pathway, known to be involved in gastric, colon, and non-small cell lung cancer.<sup>6</sup> Stacchiotti, in 2010, also described the treatment of four patients found to have recurrent disease with dedifferentiation to DFSP-FS. Three of these were treated only with imatinib and succumbed to their disease. The fourth patient followed the path of the first three described, eventually receiving chemotherapy with epirubicin and ifosfamide. Disease progression continued under this regimen and the patient was restarted on imatinib with

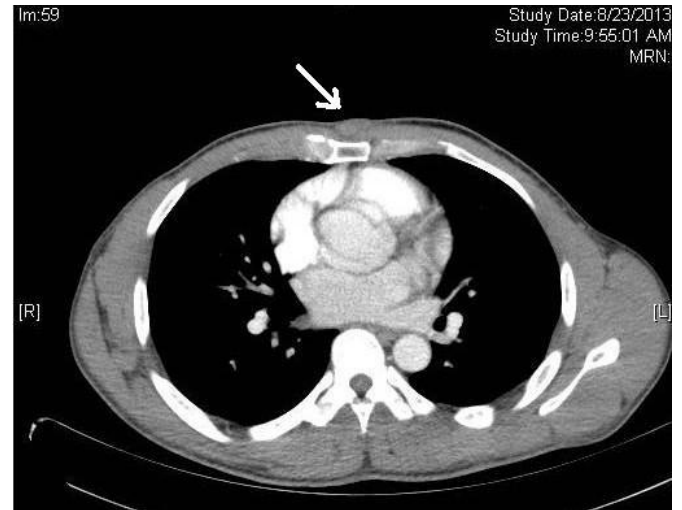
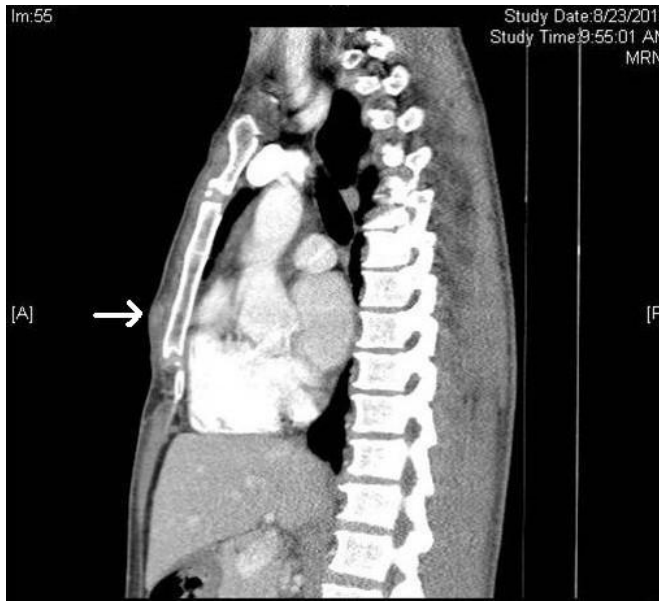
10mg of everolimus daily. This combination produced an arrest of disease progression, but was stopped due to side effects after four months of treatment.<sup>14</sup>

Further investigation of these tumors revealed that these DFSP-FS were subject to autophagy and senescence known to require functional p53 and p16. The tumors described all showed receptor tyrosine kinase activity (RTK) with PDGFR $\beta$  and PDGFR $\alpha$  activity, not responsive to imatinib. Using real time-PCR, the PDGFR $\beta$  was less active than those tumors receptive to imatinib. RTK's downstream effectors, namely AKT, ERK1/2, RSK, mTOR, S6, and 4EBP1 were examined and no mutation in these were found between cases. This suggested a ligand-independent activation of the COL1A1-PDGFR $\beta$  pathway. Although mTOR remained activated, the effects of everolimus were pronounced and aided in delaying the disease.<sup>14</sup>

DFSP is radiosensitive and radiation therapy has been used for both primary and locally recurrent DFSP. This may be helpful for cases of microscopically positive margins. Lindner described 35 patients treated from 1975 through 1996 with DFSP or DFSP-FS with microscopically positive margins whom underwent re-excision, 28 with wide margins, 6 with marginal margins and 1 with intralesional margins. Those with wide margins experienced control after excision with negative margin. Four patients with inadequate margins received adjuvant radiation therapy (median 57.5 Gy, range 50 to 65Gy) with achievement of local control. Three other patients underwent additional surgery which resulted in cure.<sup>9</sup> Ballo investigated 19 patients treated with radiation alone (n=1) or in combination with surgery (n=18). The single patient treated with radiation was a case of recurrent disease, ultimately the treatment was unsuccessful and the patient died of complications related to DFSP 21 months after treatment at MD Anderson Cancer Center. Two patients received neoadjuvant radiotherapy (50Gy) prior to surgery and experienced local control. 16 patients underwent surgery prior to radiation therapy (six with positive margins, ten with negative) and received a median of 59Gy (range 50 to 66Gy) to achieve local control.<sup>9</sup>

Suit presented the cases of eighteen patients treated with radiation therapy at Massachusetts General Hospital Radiation Oncology Department. Three patients underwent radiation alone and an additional 15 treated with surgery followed by radiation (range 50 to 78Gy). The three patients treated solely with radiation achieved local control. Those treated with surgery and radiation achieved local control in twelve of the fifteen treated, with the three undergoing successful salvage (surgical) therapy.<sup>15</sup> Between 1974 and 2012, 28 patients with DFSP were treated at Gulhane Military Medical Academy Radiation Oncology Department. Three patients received radiation therapy alone due to comorbidities or unresectability of the tumor, the remainder of the patients received postoperative therapy (median 63Gy, range 50 – 70Gy). 11 of the postoperative patients required therapy due to recurrence of the tumor, fourteen because of positive margins. The five year overall survival for all 28 patients was 93%, Five year recurrence-free survival was 89% if treated with wide excision and 74% if limited excision used (p <0.05). Two of the patients with positive margins succumbed to pulmonary metastases.<sup>17</sup>

Of further interest in research is deactivation of mTOR and the optimal dosing of imatinib for the treatment of DFSP and DFSP-FS.<sup>13,14</sup> Although surgical excision is the mainstay of treatment for DFSP, the question of treatment for recurrent and dedifferentiated tumors unresponsive to standard therapy, including imatinib, remains. However, hope now exists for patients with recurrent or locally aggressive disease which may cause disability if wide excision is attempted. Due to the high rate of recurrence, any patient with DFSP must be monitored for local recurrence.



Images above corresponding to the study performed in August 2013 showing anterior chest wall tumors without invasion. Left image 18 to 24 Hounsfield units, image right 42 Hounsfield units.

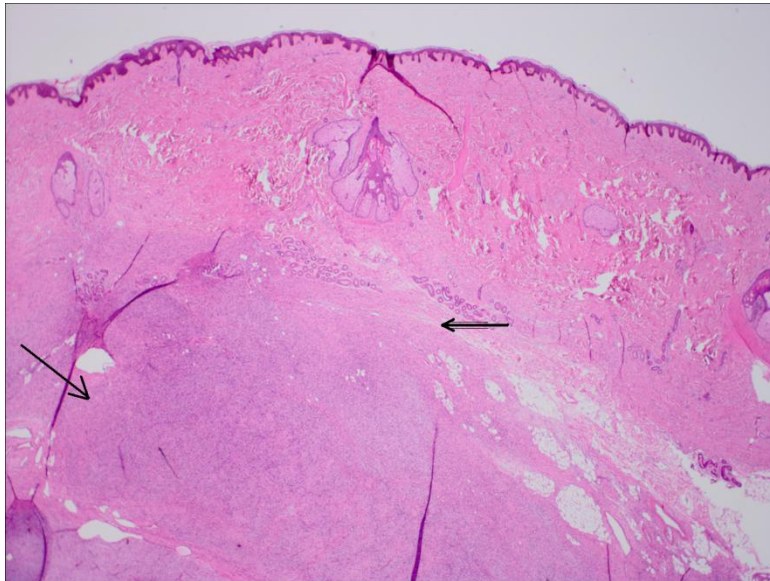


Image above from pathological examination. The arrow corresponds to the DFSP tumor in storiform pattern. The doubled arrow marks the location of the tumor invading into subcutaneous fat. Above is normal epithelium and dermis with sebaceous glands appreciable in center of the image.

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