Sustained complete remission of metastatic dermatofibrosarcoma protuberans with imatinib mesylate

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Dermatofibrosarcoma protuberans (DFSP) is a soft tissue tumor which may recur locally and rarely causes metastases to vital organs. DFSPs have specific chromosomal abnormalities involving the platelet-derived growth factor β-chain locus (*PDGFB*) which may render these tumors responsive to targeted therapy with the tyrosine kinase inhibitor imatinib mesylate. A patient with locally recurrent and metastatic DFSP resistant to first-line chemotherapy was treated with imatinib mesylate 400 mg/day. The tumor was examined by a novel fluorescence *in situ* hybridization (FISH) method for specific rearrangements of the *PDGFB* locus. The patient was followed for response and toxicity by physical examination and imaging studies. FISH revealed *PDGFB* rearrangement indicative of multiplication of the *PDGFB* fusion locus within a ring chromosome. Physical examination showed response within the first month of treatment, and subsequent computed tomography and fluorodeoxyglycose positron emission tomography documented complete response to imatinib therapy. Our patient is now in sustained complete remission for 20 months with minimal toxicity. We conclude that sustained complete remission of metastatic DFSP with specific FISH abnormalities involving the *PDGFB* locus can be obtained with imatinib mesylate with minimal toxicity for the patient. *Anti-Cancer Drugs* 16:461–466 © 2005 Lippincott Williams & Wilkins.

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Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumor of intermediate malignant potential [1]. DFSP usually presents as a nodular cutaneous mass on the trunk or proximal extremities, with equal gender frequency. The tumor usually infiltrates the s.c. tissue, resulting in a high propensity for local recurrence. However, metastases are unusual, except in the case of fibrosarcomatous differentiation. Therefore, wide local surgical excision is considered the current standard of care.

Histologically, DFSP is a cellular spindle cell neoplasm that exhibits a storiform architectural pattern and infrequent mitotic figures. The cells are typically immunoreactive for the CD34 antigen. DFSP is a soft tissue sarcoma with specific chromosomal abnormalities, typically involving rearrangements of chromosomes 17 and 22, which is manifested either by a balanced translocation t(17; 22)(q22; q13) or by supernumerary ring chromosomes containing several copies of the t(17; 22) breakpoint region. The t(17; 22) translocation juxtaposes the collagen type 1a1 (*COL1A1*) locus on chromosome 17 with the platelet-derived growth factor β-chain (*PDGFB*) locus on chromosome 22, bringing the *PDGFB* under control of the active *COL1A1* promoter and creating an autocrine loop involving activation of PDGFRB by the overexpressed PDGFB [2,3].

Although up to 50% of DFSPs recur locally, only a minority of cases develop a high-grade fibrosarcomatous histology and/or metastasize distantly, particularly to the lungs. *In vitro* evidence suggests that when the *COL1A1–PDGFB* fusion gene was expressed in a stable NIH 3T3 cell line this led to morphological transformation and increased growth rate of the cells. Cells transformed with the *COL1A1–PDGFB* gene as well as cell cultures derived from patients with DFSP are inhibited by the tyrosine kinase inhibitor imatinib mesylate (Gleevec or STI-571; Novartis, Basel, Switzerland) [4,5].

Two previous reports have described differential responses of patients with metastatic DFSP to imatinib mesylate [6,7]. In this report, we describe our own experience with a patient with metastatic DFSP refractory to first-line chemotherapy who has been in complete remission for over 20 months on imatinib mesylate.

Patients and methods

A 48-year-old woman presented in 1990 with a 3-cm nodule in the upper part of her back which was

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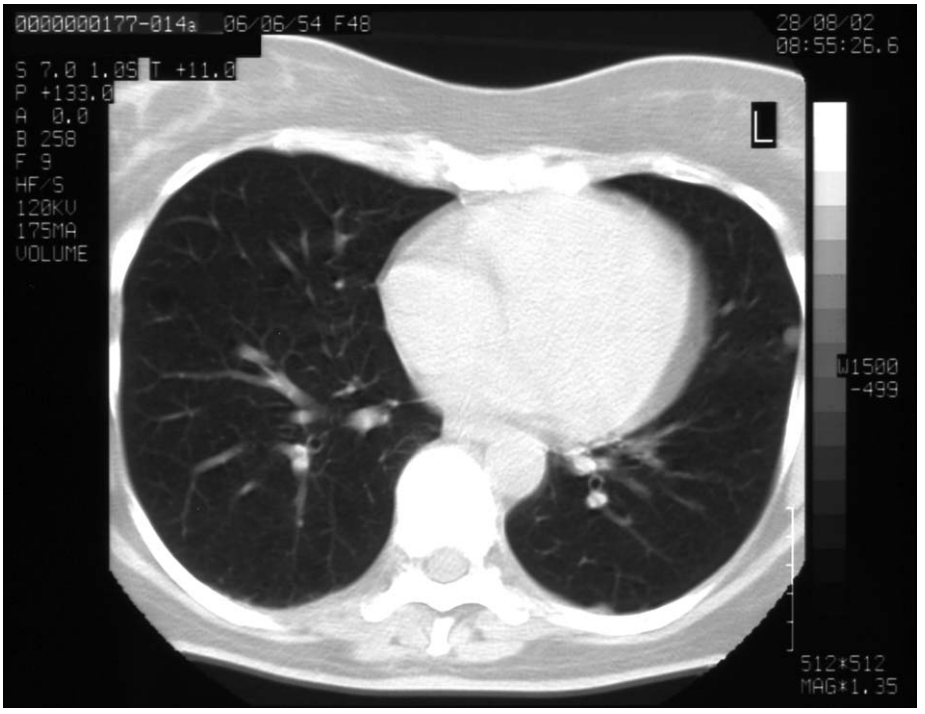
completely excised at that time. In April 2001 she presented with a similar nodule in the same area; the lesion was surgically removed. The histopathologic examination revealed a $7 \times 2 \times 3$-cm mass accompanied by a satellite lesion of 1.3 cm exhibiting low-grade spindle cell proliferation (three to five mitoses per HPF) in a typical storiform pattern diagnostic of DFSP. Immunohistochemical studies showed that the spindle cells were positive for CD34 and vimentin. In March 2002, she presented with a new local recurrence which again was surgically excised, but the status of the margins could not be assessed. At this time the histology showed transformation to a high-grade fibrosarcomatous DFSP with nuclear atypia and a high mitotic index (10 mitoses per HPF). One month later she noticed a mass in her right axilla which was biopsied. The histopathologic exam showed a 5-cm mass with features consistent with a high-grade DFSP; one (of six lymph nodes) also removed during the biopsy procedure exhibited capsular invasion by direct extension of the DFSP.

At that time the patient was referred to our clinic. The family history was notable for breast cancer in her mother and aunt. Her physical exam showed a palpable, firm, non-tender, 2×2-cm lesion in the right upper back at the site of the previously removed DFSP. Staging chest CT showed three distinct bilateral nodular lesions, the biggest of which was a pleural-based 8-mm nodule in the left lower lobe between the lingula and the anterior left lower lobe (Fig. 1), with the other two being around 5 mm each and located in the middle right lobe. Abdominal CT showed an ovary cyst; bone scans were negative and a fluorodeoxyglycose positron emission tomography (FDG-PET) scan showed increased uptake of the ^{18}FDG in both upper back paravertebral and right axilla dorsal consistent with neoplastic proliferation (Fig. *2* showing right axilla increased FDG activity). The lung lesions did not exhibit FDG avidity most likely since they were too small for the resolution of the FDG-PET scanner

The ovary cyst was surgically removed and histology was consistent with a serous cyst.

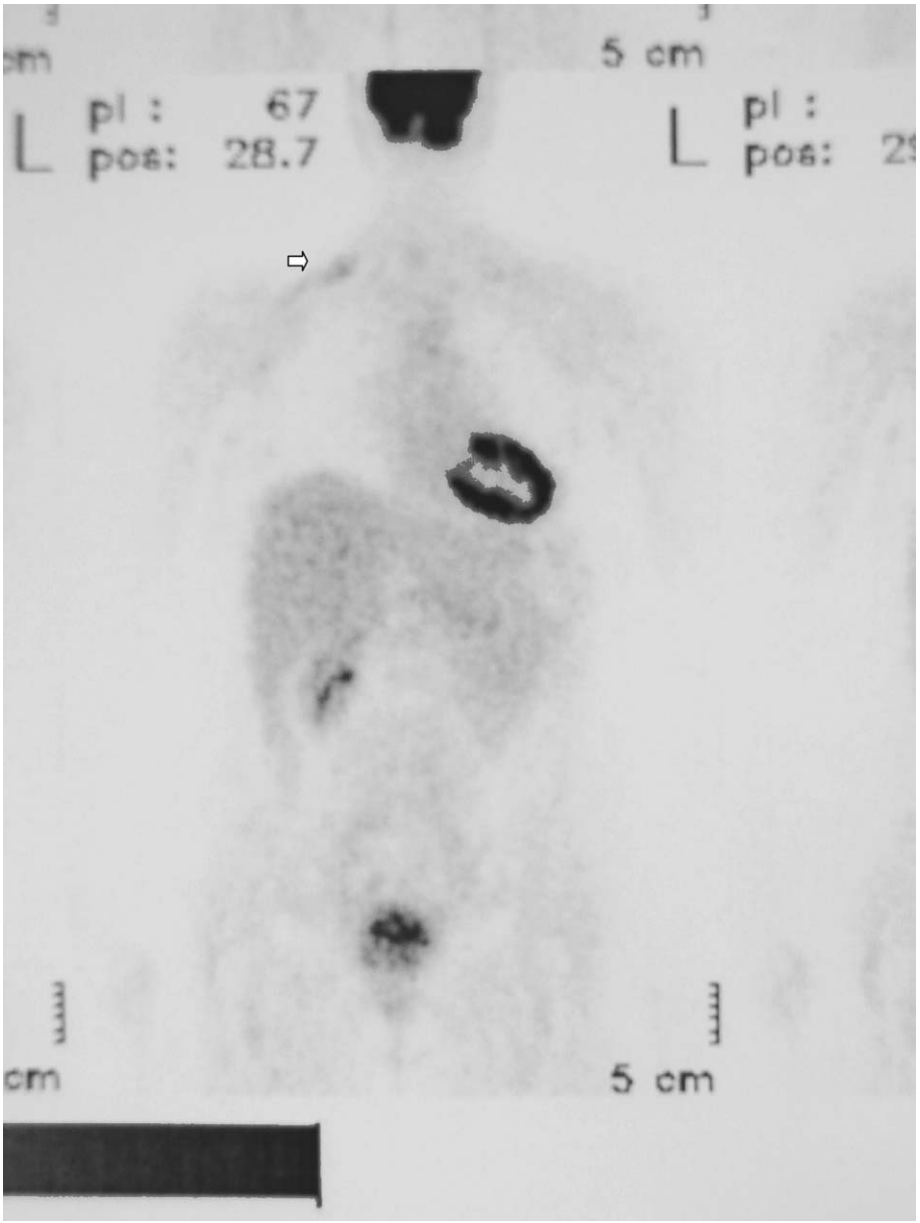
After informed consent the patient was initially treated with a combination chemotherapy regimen protocol of the Hellenic Cooperative Oncology Group, HECOG for high-grade soft tissue sarcoma, which consisted of three cycles of ifosphamide 5.6 g (total dose) on day 1 and day 2 along with MESNA plus liposomal doxorubicin (total dose) 66 mg on day 1. She developed grade 3 neutropenia (by WHO criteria) and restaging after the end of the third cycle showed a persistent palpable nodule at the her back of 2×2.4 cm and unchanged radiographic appearance of the three lung nodules.

Fig. 1



CT scan performed after three cycles of chemotherapy showing left lingula pleural-based nodule.

Fig. 2



FDG-PET scan showing (arrow) increased ^{18}FDG avidity at the right dorsal axilla.

Having no evidence of response after first-line chemotherapy and as available medical literature showed promising results of imatinib mesylate for DFSP, informed consent was obtained from the patient; imatinib mesylate was initiated at 400 mg as a single dose daily. The patient was then followed clinically with complete blood counts and biochemical panels.

^{18}FDG-PET

FDG-PET scans were obtained, in the same center, before initiation of imatinib and after 14 months on imatinib

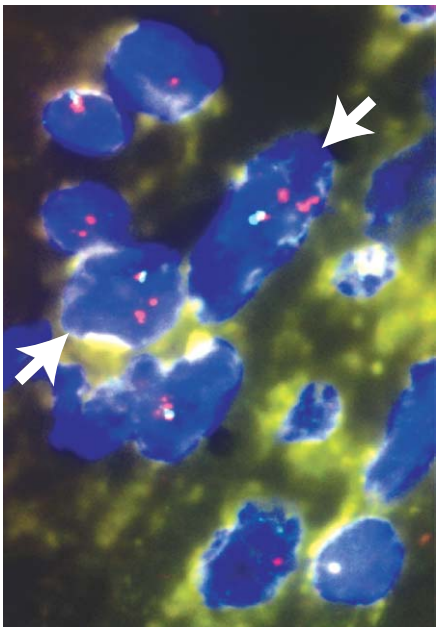
Immunohistochemistry

Review at our center of the slides from excised DFSP showed fibrosarcomatous differentiation with more than five mitoses per HPF. Paraffin-embedded, formalin-fixed sections were evaluated by immunohistochemical analysis for KIT expression (Clone A 4502/DAKO) without antigen retrieval. Sixty percent of the neoplastic cells showed dot-like cytoplasmic positive stain for KIT.

Fluorescence *in situ* hybridization (FISH)

FISH was performed by labeling bacterial artificial chromosomes centromeric (RP11-1149B8 and RP11-348I17) and

Fig. 3



Dual-color *PDGFB* FISH showing *PDGFB* rearrangement in most cells. Arrows indicate two cells in which a normal chromosome 22 (red–green paired signals) and an abnormal ring chromosome (cluster of red signals) are seen. The full complement of FISH signals is not seen due to the nuclear slicing effect in a 4-μm section and because the image conveys a single plane of focus.

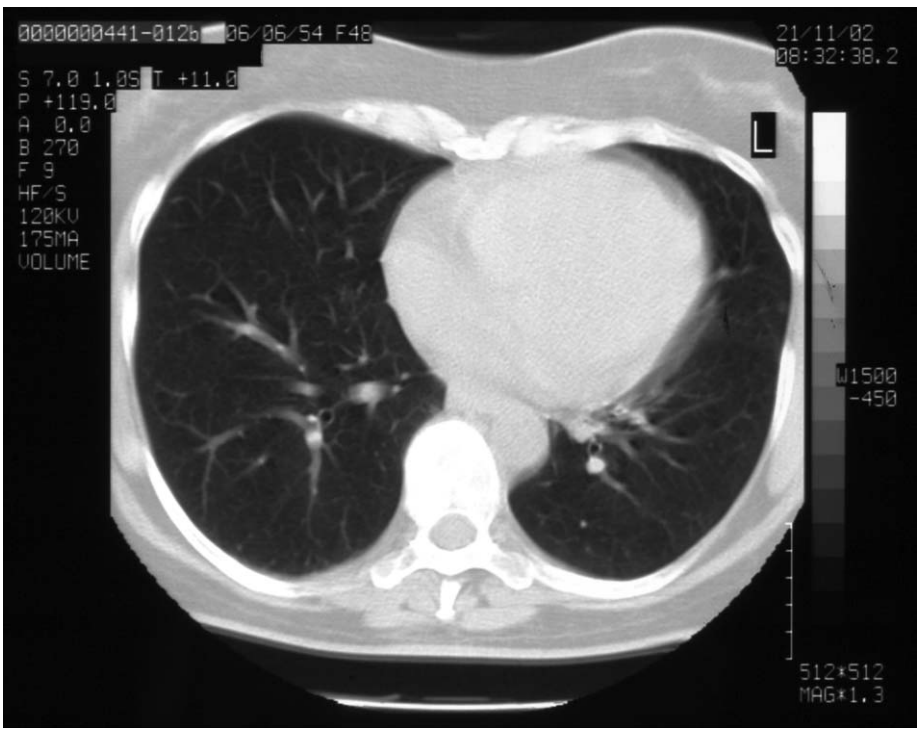
telomeric (RP11-101B10 and RP11-434E5) to the *PDGFB* locus with biotin and digoxigenin, respectively. BAC DNA isolations and random priming labeling were performed as described previously [8], and these probes were co-hybridized with Cot-1 DNA to block repetitive DNA sequences. Paraffin DFSP sections (4 μm) were pretreated first by microwaving and then by digestion with Digest All-III (Zymed, South San Francisco, CA), before proceeding with denaturation and probe hybridization. Detection of the biotinylated and digoxigenin-labeled probes was with streptavidin–Alexa 594 (Molecular Probes, Eugene OR) and FITC–anti-digoxigenin (Roche, Indianapolis, IN), respectively.

Results

PDGFB FISH evaluation of a pre-imatinib mesylate DFSP biopsy revealed *PDGFB* rearrangement in 87 of 100 nuclei. Most nuclei had two normal FISH signals (red–green pairs, indicative of the non-rearranged PDGFB locus on chromosome 22), accompanied by a cluster of two to three abnormal FISH signals (red only) indicative of multiplication of the *PDGFB* fusion locus within a ring chromosome (Fig. 3).

One month after initiating imatinib mesylate, the physical examination showed a dramatic tumor response with disappearance of the palpable back lesion. Three

Fig. 4



CT scan after 3 months on imatinib mesylate showing resolution of the left lingula lesion.

months after the starting of imatinib mesylate, a CT of the chest showed resolution of the three lung nodules (Fig. 4). Having obtained clinical and radiographic complete remission on imatinib mesylate 400 mg daily, she continued this regimen with clinical monitoring every month for the first year and every 3 months thereafter.

Toxicity from imatinib has been only grade 1 edema and grade 1 anemia with macrocytic indices as previously described for imatinib, along with a slight elevation of transaminases (AST and ALT), and lactic dehydrogenase not requiring dose reduction.

Re-evaluation with chest and abdominal CT after 14 months of imatinib mesylate showed no evidence of disease. A FDG-PET scan at that time was also negative for apparent disease activity. She has now remained in clinical complete remission for over 20 months on imatinib mesylate 400 mg/day, with a performance status of 0 (ECOG scale).

Discussion

Surgical resection remains the standard of care for DFSP, but there is a risk of recurrence and about 5% of patients with DFSP will go on to develop metastatic disease. We describe our experience with a patient with metastatic DFSP resistant to first-line chemotherapy who has now maintained complete remission for 15 months on imatinib 400 mg daily. The rationale for the use of this targeted therapy was the previously reported data on COL1A1–PDGF-transformed cells being growth inhibited by imatinib. Also, at the time that imatinib was initiated, one abstract was available from ASCO 2001, reporting promising results in patients with metastatic DFSP treated on Gleevec [9].

The case reported herein is the first in which an imatinib clinical response has been shown in a DFSP with documented *PDGFB* rearrangement. The *PDGFB* FISH analysis demonstrated three copies of the rearranged *PDGFB*, which is typical for the tandemly repeated *COL1A1–PDGFB* fusion oncogenes in DFSP ring chromosomes. This oncogenic mechanism results in PDGFB overexpression, with consequent PDGFRB activation, and stimulation of cell mitogenic and survival pathways [2]. Imatinib therapy presumably interrupts the PDGFB autocrine loop by inhibiting PDGFRB activation [4,5]. On clinical grounds, after 20 months on imatinib 400 mg daily our patient is fully active, back to her work and has sustained only grade 1 toxicity which did not require discontinuation or dose reduction of her treatment. This is the longest experience of continuous treatment of metastatic sarcomatous DFSP on imatinib published so far.

As expected from previous experience both from chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST), the clinical response was evident within the first month of treatment [10].

There are two published reports describing responsiveness of metastatic DFSP to imatinib [6,7], but two of the three patients reported so far had only a transient response and our patient is in complete remission for 20 months now. These preliminary findings raise the question as to what additional factors might influence the degree of imatinib response in DFSP. One possibility is that only a subset of the neoplastic cells in some DFSP contain the *PDGFB* oncogenic mechanism and are thereby susceptible to imatinib mesylate. In the case reported herein, FISH analyses demonstrated *PDGFB* rearrangement in most or all of the neoplastic cells. Another possibility is that some DFSP cells, despite having *PDGFB* activation, develop resistance to imatinib either due to activation of parallel signaling pathways or due to acquisition of resistance mutation in the *PDGFB* receptor. Similar mechanisms are implicated in the resistance of *bcr–abl*-positive CML to imatinib [11]. Many DFSP contain additional clonal cytogenetic aberrations, beyond the diagnostic ring chromosomes, and these might provide redundancy in the growth survival pathways inhibited by imatinib. Additionally, since there are variations in the translocation sites in the *COL1A1* gene seen in DFSP cases, there might be different levels of PDGF activation amongst DFSP. A further delineation of the FISH status of these cases and molecular characterization may reveal a molecular signature of imatinib-responsive DFSP. In GIST there is evidence that mutations in exon 11 of c-*kit* (juxtamembrane region of transmembrane KIT receptor) render these tumors more responsive to imatinib in contrast to wild type c-*kit* GIST or mutations in exon 9 which are associated with relative resistance to imatinib [12]

The evidence for varying clinical responses (present study and [6,7]) emphasizes the need for an international effort to systemically study imatinib response in metastatic DFSP. Pertinent questions include whether clinical response is influenced by the extent and molecular nature of *PDGFB* activation, and by the dose and schedule of imatinib since so far the dose and schedule are based on experience from other tumors.

A recent review article on targeted therapy of DFSP with imatinib mesylate has been published where more data on patients treated with this approach are described [13].

The optimal duration of treatment in patients who respond to imatinib is another unknown factor at this point. A recently announced study in GIST patients suggests that imatinib should be continued indefinitely in

responding patients since discontinuation after 1 year of treatment led to re-progression within 3 months in five of 21 patients [14]. Our patient has so far tolerated imatinib very well, but issues of cost in view of a limited health care budget are of concern. The new era of targeted based oncology will require the international collaboration of many specialists and novel approaches by the health care community for the benefit of our patients.

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