Effectiveness of Imatinib Mesylate Treatment in a Patient with Dermatofibrosarcoma Protuberans with Pulmonary and Pancreatic Metastases

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Abstract

We herein encountered a case of abdominal wall dermatofibrosarcoma protuberans (DFSP) that developed pulmonary and pancreatic metastases 5 years after complete resection. Because specific rearrangements of the platelet-derived growth factor beta (PDGFB) locus by a novel fluorescence in situ hybridization method was detected, the patient was treated with imatinib mesylate at 400 mg/day. A partial response was achieved by imatinib without any specific toxicity. Although metastatic DFSP is an extremely rare disease, an evaluation of PDGFB fusion is essential and imatinib mesylate should be considered as an optimal therapeutic choice in patients with metastatic or locally advanced DFSP.

Key words: imatinib, metastatic DFSP, FISH, PDGFB fusion gene

(Intern Med 55: 2507-2511, 2016)
(DOI: 10.2169/internalmedicine.55.6836)

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare, fibrohistiocytic tumor of the skin and subcutaneous tissue. The disease occurs more frequently on the trunk than proximal extremities and rarely in the head and neck region (1, 2). Cytogenetically, DFSP is characterized by a pathognomonic translocation t(17;22) (q22;q13) with fusion of the collagen type A chain (COL1A1) gene on chromosome 17 with the platelet-derived growth factor beta chain (PDGFB) gene on chromosome 22 (3, 4). This results in the constitutive expression of the PDGFB ligand, creating an autocrine stimulatory loop that drives cell proliferation and fibrosis.

Standard treatment for DFSP includes complete resection of a 2-3 cm wide margin of visibly uninvolved tissue, including underlying fascia (1-3). In general, DFSP has a low malignant potential, however, it has a pronounced tendency for local relapse (1-3, 5, 6). In addition, distant metastases are extremely rare, but there have been occasional reports of distant metastases and a poor prognosis (5-11).

Imatinib mesylate is a molecularly targeted drug that inhibits ABL tyrosine kinase and several type III tyrosine kinase receptors, including PDGFB. Thus, imatinib therapy is a good option for unresectable, recurrent, or metastatic DFSP. Several clinical studies have demonstrated the efficacy of imatinib (12-14), however, little information is available regarding the usefulness of imatinib in Japanese patients with metastatic DFSP (15-18). We encountered a case of abdominal wall DFSP that developed pulmonary and pancreatic metastases 5 years after complete resection. The patient was treated with imatinib mesylate 400 mg/day and a partial response (PR) was achieved and a long disease-free survival has been obtained. We herein describe a rare case of pulmonary and pancreatic metastases of DFSP successfully treated with imatinib mesylate in a Japanese patient along with a review of the literature.

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Received for publication November 15, 2015; Accepted for publication January 11, 2016
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Case Report

A 49-year-old man had undergone complete resection of a giant DFSP tumor (approximately 10×10 cm) with skin grafting on his upper abdomen. Although routine follow-up was repeated after the operation, chest radiographs revealed an abnormality at 5 years after the operation. He was referred to our hospital for further examination. Computed tomography (CT) revealed a mass in the left lower lobe of the lung and a pancreatic mass (Fig. 1). A physical examination revealed no remarkable abnormalities except the large surgical scar on the abdomen (15×25 cm). Laboratory findings showed no abnormalities, including tumor markers. 18F-Fluorodeoxy glucose positron emission tomography (FDG-PET) was performed and showed an accumulated uptake in the pulmonary and pancreas masses. No other areas showing an abnormal uptake on FDG-PET were observed. An ultrasound-guided needle biopsy for the pancreatic mass was performed by gastric fiberscopy. The histological findings revealed that the tumor was composed of spindle cells arranged in a storiform and herringbone pattern (Fig. 2A). The histological findings indicated that the lesion was predominantly composed of spindle-shaped cells, which were diffusely positive for CD34 on an immunohistochemical analysis (Fig. 2B-D). In addition, a COL1A1-PDGFB translocation was detected in both the primary and pancreatic tumors with a dual fluorescence in situ hybridization (FISH) fusion probe set (Fig. 3), consistent with metastatic DFSP. Although a histological analysis for the pulmonary lesion was not performed, the radiographic finding suggested pulmonary metastasis. The patient was initially treated with three cycles of cisplatin (day 1) and doxorubicin (day 1) every 3-4 weeks. However, the metastatic DFSP tumors were resistant to chemotherapy. The patient was then treated with imatinib mesylate at 400 mg/day. Both pulmonary and pancreatic tumors showed significant reductions (Fig. 4), compatible with a PR by imatinib. The patient has remained well for approximately 1 year after the initiation of imatinib without any specific toxicity.

Discussion

Distant metastases have been reported to occur in 1-6% of DFSP patients and typically develop after multiple local recurrences (5, 6). According to the pertinent literature, the major sites include the lungs, followed by the brain (5-14). Pancreatic metastasis of DFSP is extremely rare, with only two other reported cases identified in the PubMed database using the search terms “DFSP” and “pancreas” or “distant metastasis” (9, 10). We found an autopsy case showing multiple metastatic lesions, including the lung and pancreas, however, the clinical manifestations were lung and brain metastases (11). To the best of our knowledge, there have been no previous case reports clinically presenting combined pulmonary and pancreatic metastases in patients with DFSP. In addition, it has been reported that DFSP with fibrosarcomatous (FS) components may have an increased metastatic potential compared to DFSP without FS areas, resulting in an aggressive clinical outcome (19, 20). However, there was no FS area, at least in the specimens taken from the pancreas, in the present case.

Rutkowski et al (12), summarized two distinct phase II trials of imatinib (400-800 mg daily) in patients with locally advanced or metastatic DFSP that were positive for PDGFB fusion. The response rate to imatinib was 46%. The presence of the molecular target (COL1A1-PDGFB fusion) appears to be a marker of responsiveness to imatinib treatment in DFSP patients (12-14), although the response is not always consistent with the presence of COL1A1-PDGFB fusion. However, it has also been shown that FS-DFSP lacking the specific aberration does not respond to imatinib treatment (13, 14). Thus, an examination of the presence of COL1A1-PDGFB fusion in each case is critical before initiating imatinib therapy, as shown in the present case. According to these clinical trials and molecular studies, imatinib has been
Figure 2. Histological appearance of the pancreatic specimen. Microscopically, the tumor was composed of spindle cells arranged in a storiform and herringbone pattern. (A) Hematoxylin and Eosin staining, 200×. Immunohistochemical staining revealed that tumor cells were strongly positive for CD34 (B) and negative for S100 (C) and α-SMA (D).

Figure 3. A fluorescence in situ hybridization (FISH) analysis using the platelet-derived growth factor B gene (PDGFB) probe on tumor cells showed the presence of PDGFB break apart signal (arrows).

was not always consistent with a good response to imatinib, the obtained clinical outcomes were promising and similar to the results reported from other countries (12-14). Several clinical studies and case reports (3, 12-18) suggested that that a moderate dosage of 400-600 mg/day appeared to be as equally as effective as a higher dosage (800 mg/day) and was better tolerated. Since our case responded to 400 mg of imatinib without any toxicity, the therapy was continued with the same dosage. Thus, further clinical investigations of imatinib for the treatment of Japanese patients with advanced and metastatic DFSP are warranted especially with a focus on the presence of COL1A1-PDGFB fusion and the optimal dosage of imatinib.

Wide surgical excision is the standard curative treatment for localized DFSP but may result in cosmetic disfigurement or functional impairment (1-3, 5, 6). Several recent studies and case reports indicated that the neoadjuvant use of imatinib in locally advanced DFSP was efficacious to reduce the tumor size before surgery (21, 22). Thus, pretreatment with imatinib could avoid wide excision for definitive surgery. In the present case, surgical resection was performed with negative margins, however, the initial tumor size was 10×10 cm. To the best of our knowledge, no information is available regarding the relationship between the resected tumor size of DFSP and local relapse and/or distant metasta-
sis. However, the present case suggested that the initial huge size was related to the subsequent development of distant metastasis after surgery. Thus, in cases with relative large DFSP lesions, neoadjuvant imatinib therapy could be considered as an alternative strategy before surgery.

In conclusion, the present case demonstrated that imatinib is a useful agent for metastatic DFST even in Japanese patients. Distant metastasis is a rare clinical manifestation and metastatic DFST is an extremely rare disease in clinical practice. Thus, we should be aware that treatment with imatinib can be an optimal therapeutic choice in patients with DFSP.

The authors state that they have no Conflict of Interest (COI).

References


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