OBSERVATION

A Case of Cutaneous Rosai-Dorfman Disease Refractory to Imatinib Therapy

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Background: Rosai-Dorfman disease is a non–Langerhans cell histiocytosis that recently has been treated successfully with imatinib mesylate in a patient with a systemic variant of the disease.

Observations: We describe a 69-year-old man with cutaneous Rosai-Dorfman disease manifesting as progressive, deeply infiltrated skin lesions. Histopathologic examination of the lesions demonstrated dense dermal infiltrate positive for CD68, stabilin-1, and S-100, but not for CD1a. The histiocytes were positive for platelet-derived growth factor receptor α, the target molecule for imatinib. During the 5-year course of the disease, multiple therapeutic approaches (tuberculostatic drugs, topical and systemic glucocorticoids, thalidomide, isotretinoin, and methotrexate) did not result in significant improvement. Imatinib mesylate therapy (600 mg/d for 2 1/2 weeks and then 400 mg/d for 10 weeks) had no effect, despite the expression of platelet-derived growth factor receptor α on the histiocytes.

Conclusions: Failure of imatinib therapy in our patient may be due to a lack of functioning target molecules, the therapy protocol, or the course of the disease. Cutaneous and systemic variants of Rosai-Dorfman disease may be different clinical entities or at least may respond differently to tyrosine kinase inhibitors.

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ROSAI-DORFMAN DISEASE (RDD) is a non–Langerhans cell histiocytosis and was first described by Rosai and Dorfman in 1969.1 Because the disease primarily involves lymph nodes, it is also known as sinus histiocytosis with massive lymphadenopathy. Extranodal manifestations have been reported in 43% of cases, most frequently affecting the skin.2 A cutaneous variant of RDD (C-RDD) was reported for the first time in 1978 by Thawerani et al.3 Since then, about 75 cases of C-RDD have been reported.4 Histologically, RDD is characterized by histiocytes with large vesicular nuclei and abundant cytoplasm. These cells are positive for markers typical in monocytes and macrophages (eg, CD68) and in dendritic and Langerhans cells ($100), while being negative for CD1a.3–4

Despite the clear histologic features, the clinical diagnosis of C-RDD is difficult because of a variable clinical appearance without lymphadenopathy. Most lesions are located on the face, followed by the back, chest, thigh, flank, and shoulder. Clinically, the morphologic structure of lesions ranges from nodules, pustules, and papules to plaques and patches.4 It has been suggested that C-RDD and systemic (S-RDD) variants of the disease are distinct clinical entities.3–5 Cutaneous RDD has a median age at onset of 43.5 years, shows a female preponderance (2:1), and predominantly affects persons of Asian and white race/ethnicity. In contrast, the median age at onset of S-RDD is 20.6 years, it occurs slightly more often in men (1.4:1), and patients are rarely of Asian race/ethnicity.5 Treatment of S-RDD is challenging. Because it is characterized as a benign, self-limiting disease, therapeutic approaches tend to be less aggressive. For example, the use of systemic glucocorticosteroid and antibiotic regimens, as well as cryotherapy, surgical excision, and radiation therapy for localized lesions, has been described.7 Case reports have documented the use of interferon alfa8 or acyclovir.9 Treatment options for C-RDD include surgery, liquid nitrogen, radiation therapy, and glucocorticosteroid or thalidomide regimens.9

Utikal and colleagues10 described a patient with complete remission of S-RDD after receipt of imatinib mesylate therapy.
Therefore, we decided to use this drug in a patient with refractory C-RDD.

**REPORT OF A CASE**

A 69-year-old white man with an otherwise unremarkable medical history had developed progressive, deeply infiltrated skin lesions on the trunk and the upper and lower limbs in 2002. At the initial examination in 2006, we noted deeply infiltrated patches and plaques of dark red to light brown up to 25 cm in diameter that had begun in the gluteal region and later spread to the trunk and the limbs (Figure 1A and B). Hematoxylin-eosin staining of skin biopsy specimens revealed a dense dermal infiltrate, composed mainly of histiocytes and plasma cells, which extended into the subcutis (Figure 2). Lymphocytes were seen within the cytoplasm of these histiocytes (emperiploisis). The cells of the infiltrate were positive for CD68, stabilin-1, and S-100, but not for CD1a. Additional immunohistochemical stainings documented that the histiocytes were positive for platelet-derived growth factor receptor α (PDGFRα) (Figure 3), but not for PDGFRβ or macrophage colony-stimulating factor receptor (data not shown), all of which are target molecules of imatinib.11-13 Successive magnetic resonance images and computed tomographic scans showed skin infiltrates but no organ involvement (Figure 1C). All routine laboratory variables were within normal ranges.

During the 5-year course of the disease, the patient had received various treatments without significant improvement, including tuberculostatic drugs, glucocorticosteroids (topical and systemic), thalidomide, isotretinoin, and methotrexate. In 2004, radiation therapy (24 Gy) was performed on symptomatic plaques in the sacral region and on the back and the arms.

Because of the PDGFRα positivity of the tumor cells, imatinib mesylate (Gleevec; Novartis, Basel, Switzerland) therapy was started at a dosage of 600 mg/d. The patient experienced constipation and spasmodic abdominal pain, which are known adverse effects of imatinib me-

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*Figure 1.* Infiltrated patches and plaques of dark red to light brown of the gluteal region (A) and the lower left arm (B) before treatment with imatinib mesylate. Sagittal plane of T1-weighted magnetic resonance images (C and D) with fat suppression and intravenous contrast medium of the lower left arm before (C) and after (D) treatment with imatinib. The tumor (arrows), also seen in B, measures approximately 5.7 × 0.8 cm.
sylate therapy, so the dosage was reduced after 2½ weeks to 400 mg/d, which was well tolerated and was continued for 10 more weeks. No significant response was detected after the 12½ weeks of imatinib therapy clinically or by magnetic resonance imaging of the marker lesions on the forearm. Therefore, imatinib treatment was discontinued.

COMMENT

Utikal et al\textsuperscript{10} successfully treated a patient having S-RDD with imatinib. In contrast, C-RDD in our patient was completely resistant to this treatment.

Imatinib is a tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukemia, eosinophilia, gastrointestinal stromal tumors, and dermatofibrosarcoma protubers. It inhibits the tyrosine kinases BCR-ABL, PDGFR\textsubscript{α} and PDGFR\textsubscript{β}, and Kit. Low dosages of imatinib mesylate (100 mg/d) are effective in diseases associated with the \textit{FIP1L1-PDGFRα} tyrosine kinase, a “gain-of-function” mutation due to an 800-kb deletion on chromosome 4q12, which can be found in some cases of hypereosinophilic syndrome.\textsuperscript{14,15} Imatinib therapy is effective in diseases associated with the BCR-ABL fusion protein (such as chronic myeloid leukemia) or with PDGFR\textsubscript{β} and \textit{c-Kit} (such as gastrointestinal stromal tumors).\textsuperscript{16,17} Because imatinib also targets the macrophage colony-stimulating factor receptor, it was recommended for use in diseases in which \textit{c-fms} activation is implicated (e.g., breast and ovarian cancer and inflammatory conditions).\textsuperscript{12,18} Montella et al\textsuperscript{13} reported successful therapy of cerebral Langerhans cell histiocytosis using imatinib.

There are several possible explanations for the failure of imatinib therapy. The following are applicable in our patient with C-RDD.

TARGET MOLECULES

In our patient, skin lesions stained weakly positive for PDGFR\textsubscript{α} and were negative for PDGFR\textsubscript{β} and \textit{c-Kit}, sug-

gesting that the tumor cells might not express sufficient target molecules for imatinib therapy. In comparison, lesions in the patient treated by Utikal et al\textsuperscript{10} stained positive for the target molecules of imatinib PDGFR\textsubscript{β} and \textit{Kit}. Recently reported PDGFR\textsubscript{α} mutations, which cause resistance to imatinib,\textsuperscript{12} might also explain the failure of this drug in our patient. However, we were unable to test this hypothesis because our patient refused further investigations, believing they would be of no therapeutic benefit to him.

TREATMENT PROTOCOL

Utikal et al\textsuperscript{10} treated their patient for 10 weeks at a high dose of imatinib mesylate (600 mg/d). Because of gastrointestinal adverse effects in our patient, we had reduced the dose to 400 mg/d.

COURSE OF THE DISEASE

The course of the disease was much longer in our patient (5 years) than in the patient treated by Utikal et al\textsuperscript{10} (1½ years). Newer lesions may have higher turnover and
shorter cell cycles and demonstrate better response to imatinib therapy, which abrogates the activation of multiple signal transduction pathways.

In conclusion, our case findings suggest that C-RDD and S-RDD may be distinct clinical entities. Therefore, they may respond differently to tyrosine kinase inhibition by imatinib therapy.4,5,16

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REFERENCES