Imatinib-Induced Sweet Syndrome in a Patient With Chronic Myeloid Leukemia

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Background: Imatinib mesylate has become one of the main chemotherapeutic agents currently used to treat patients with chronic myeloid leukemia (CML). Although cutaneous reactions to this drug have been documented before, this is the first time that Sweet syndrome has been reported with its use.

Observations: We report a case of Sweet syndrome secondary to the administration of imatinib to treat CML. On 2 separate occasions, a 53-year-old African American can woman with CML developed neutrophilic dermatosis consistent with Sweet syndrome after chemotherapy with imatinib.

Conclusion: Greater awareness of the adverse effects of imatinib and the characterization of its cutaneous adverse effects will lead to improved surveillance for and treatment of those adverse effects.

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REPORT OF A CASE

A 53-year-old African American woman presented with gum bleeding in October 2000. Testing revealed splenomegaly, an elevated white blood cell (WBC) count of 158 × 10⁹/µL that rose to 190 × 10⁹/µL after 4 weeks, and a platelet count of 597 × 10⁹/µL. A peripheral blood smear showed predominant neutrophils, myelocytes, metamyelocytes, and basophils with less than 10% myeloblasts. Bone marrow showed hypercellularity with hyperplasia of granulocytic and megakaryocytic lineages, features consistent with chronic myeloid leukemia (CML). A diagnosis of CML was confirmed when the patient tested positive for the presence of the BCR-ABL fusion gene. Findings from further evaluation, which included a history and physical examination as well as laboratory tests, were unremarkable at the time of diagnosis.

Initially, the patient was treated with 1 g of hydrea twice daily from November 2000 until September 2001 at which point the patient began imatinib mesylate therapy. Her maximum tolerated daily dose of imatinib mesylate was limited to 300 mg because of gastrointestinal adverse effects, particularly abdominal pain and diarrhea. Initially, she had a good hematologic response to imatinib, but her cytogenetic response was minimal, showing BCR-ABL values of 53% compared with 69% before the start of chemotherapy. Findings of a repeated bone marrow biopsy showed no new abnormalities but were consistent with CML in the chronic phase with persistence of the BCR-ABL defect. It was decided to continue treatment with imatinib because of the patient’s refusal to undergo bone marrow transplantation. The patient was then lost to follow-up until 2003.

In November 2003, the patient agreed to restart chemotherapy with imatinib. However, soon after starting treatment, she developed an abrupt onset of painful and tender erythematous skin plaques and nodules on her upper extremities that resolved with hyperpigmentation after imatinib treatment was discontinued. This was the first time she had developed such skin lesions, and it was not immediately evident that they were secondary to imatinib therapy.

In January, chemotherapy with imatinib was restarted as part of the effort to optimize therapy, and within a week, the patient was admitted with complaints of shortness of breath and skin lesions identical to those of the prior episode. During this admission, the patient was found to have pleural and pericardial effusions. She also had a WBC count of 57 × 10⁹/µL, a platelet count of 740 × 10⁹/µL, and a single temperature spike of 38°C (100.4°F). Over the course of a week, her WBC count dropped to 52 × 10⁹/µL, but the percent-
age of mature neutrophils rose from 14% to 55%. Imatinib treatment was discontinued, and therapy with prednisone led to resolution of the skin lesions although with residual pigmentation. The patient was subsequently treated again with hydroxy for her CML.

The skin lesions of this patient manifested as an abrupt onset of tender and painful erythematous plaques and nodules limited to the upper extremities, particularly the dorsal aspects of both hands and forearms (Figure 1). The lesions were multiple, bilateral, and asymmetrical, sparing the face, neck, back, and lower extremities. The lesions healed but left residual pigmentation and were not pseudovesicular. Both outbreaks were directly preceded by the use of imatinib and involved lesions of similar appearance and distribution. A skin biopsy specimen showed neutrophilic dermatosis with epidermal sparing consistent with Sweet syndrome (Figure 2 and Figure 3). While extension into the deep dermis and subcutaneous fat (Figures 2 and 3) has been seen, it is atypical of Sweet syndrome.

The temporal association of both outbreaks with the administration of imatinib suggests causality. This is the first report of an association between imatinib and neutrophilic dermatosis. It is particularly important because the patient reported no history of skin reactions or lesions during the natural course of her CML other than after therapy with imatinib.

In addition to the skin findings, this patient had pleural and pericardial effusions, which have previously been linked to therapy with imatinib. Furthermore, the distribution of the lesions on both occasions was consistent with Sweet syndrome. Therapy with prednisone at 40 mg/d led to complete resolution, which is again consistent with Sweet syndrome. Blood cultures and bacterial, fungal, and mycobacterial cultures of the skin as well as special stains for the skin biopsy specimen failed to reveal any microbiological cause for the lesions.

**COMMENT**

Imatinib mesylate (STI 571; Gleevec; Novartis Pharmaceuticals, Basel, Switzerland), a derivative of 2-phenylaminopyridine, is a molecular antagonist of tyrosine kinase and is used in the treatment of CML because of its specific inhibition of BCR-ABL. Since this drug is used increasingly as part of the mainstay therapy for CML, characterization of its adverse effects is becoming increasingly important.

The most common adverse effects include nausea, edema, myalgias, and diarrhea, with a mild severity rating (grade 1 or 2) based on the National Cancer Institute/National Institutes of Health Common Toxicity Criteria. The present case is the first report of pathologically confirmed Sweet syndrome occurring after imatinib therapy, but it is consistent with increasing reports of adverse skin reactions. In the largest series published to date, 32% of 532 patients in the chronic phase of CML who were taking 400 mg of imatinib mesylate daily developed a rash. Four of these were deemed serious adverse drug reactions, although they were not further characterized. Another cohort of 78 subjects was observed for 15 months and showed a 12% incidence of skin rashes attributable to imatinib therapy for CML.

Previously reported data suggest a dose-response relationship for adverse cutaneous effects of imatinib; the most commonly reported toxic doses were between 400 and 600 mg daily. Our patient, however, could tolerate only 300 mg/d because of gastrointestinal adverse effects.
A variety of adverse cutaneous reactions have been described, ranging from self-limiting dermatitic rashes to erythroderma for which cessation of therapy was required. Also reported were reactions similar to graft-vs-host disease, erythema nodosum, small-vessel vasculitis, exanthematous pustulosis, and Stevens-Johnson syndrome. Sweet syndrome has been associated with chronic myeloid leukemia, but the association is rare, and the only times our patient developed skin lesions were after the administration of imatinib.

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REFERENCES