Disseminated Erythematous and Pityriasiform Plaques Caused by Imatinib Mesylate

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Sir,

Imatinib mesylate (formerly STI 571, now referred to as Glivec® in Europe and Gleevec® in the United States) is a rationally developed, orally administered potent competitive inhibitor of the BCR-ABL protein tyrosine kinase that reveals a significant efficacy and a favourable safety profile in patients with chronic myeloid leukaemia (CML) (1). This compound has been reported to be effective also in gastrointestinal stromal tumours unresponsive to standard chemotherapy (2) and in metastatic dermatofibrosarcoma protuberans (3).

We report here a patient who developed a skin rash during treatment with imatinib mesylate.

CASE REPORT

A 51-year-old female physician presented to our hospital with a 3-week history of persistent and progressive leucocytosis in consecutive laboratory tests performed because of an extrasystolic arrhythmia. She had no evidence or history of any skin disorder, complained of no symptoms and her physical examination was unremarkable. On admission, she revealed a leucocytosis of 31,900/μl (differential count: neutrophils 63, lymphocytes 17, monocytes 2, eosinophils 2, basophils 2, metamyelocytes 3, myelocytes 11) and platelet counts of 4.08 × 10^5/μl; all other haematologic, serologic and biochemical tests were within normal limits. The findings of bone marrow aspiration and biopsy were diagnostic of CML. Cytogenetic analysis demonstrated a 9;22 translocation (Philadelphia chromosome) in all metaphases examined, whereas PCR showed a BCR-ABL transcript.

The patient started imatinib mesylate therapy with an alternating dose of 200/300 mg every other day. After 2 months of treatment she experienced the sudden onset of a slightly pruritic exanthema on the trunk and extremities. She was not taking any other medication concurrently and had no history of an intercurrent infection. Physical examination revealed multiple sharply defined round or oval erythematous plaques with a diameter of 1 – 3 cm, with numerous fine scales (Fig. 1). The patient refused to take medication for her rash. However, an increase in the daily dose of imatinib mesylate to 400 mg resulted in rapid deterioration of the skin lesions, which became intensely pruritic and increased markedly in number and size. Apart from the CML-associated findings all results of laboratory investigations, including syphilis, immune and virus serology (HIV, CMV, HBV, HCV, EBV, HHV6), were within normal limits. Histological examination of biopsy specimens obtained from truncal lesions showed a focal parakeratosis, moderate acanthosis and spongiosis of the epidermis. In the upper dermis a mononuclear cellular infiltrate was present around the superficial capillaries extending from there into the epidermis.

Imatinib mesylate treatment was discontinued and oral methylprednisolone administration was initiated at a dose of 16 mg/day, which was progressively reduced to 4 mg/day within 2 weeks. The rash slowly resolved over the ensuing 3 weeks. Then methylprednisolone administration was stopped and imatinib therapy (300 mg/day) was reintroduced. Six days after readministration of the drug a recurrence of the rash was observed. Since the patient refused to discontinue imatinib mesylate therapy, a 4 mg methylprednisolone administration every second day was introduced. Under this medication, and despite further administration of imatinib mesylate, the skin lesions slowly resolved within 4 months. The patient is presently completing 13 months of imatinib mesylate therapy; she has complete cytogenetic and molecular remission of CML and reveals only residual macular cutaneous hyperpigmentation.
DISCUSSION

The efficacy of imatinib mesylate in the management of CML and advanced gastrointestinal stromal tumours has been documented in recent multicentre clinical trials (1, 4 – 6). Moreover, several case reports indicate that this compound may also be effective in metastatic dermatofibrosarcoma protuberans, which is caused by activation of the platelet-derived growth factor B receptor, a transmembrane tyrosine kinase (3, 7).

Imatinib mesylate is generally well tolerated. Its most common adverse events include oedema, diarrhoea, nausea, fatigue and myalgias, which are mostly mild or moderate (1, 4 – 6). Cutaneous side effects are observed in 17 – 38% of treated patients and only rarely is discontinuation of therapy required; both the frequency and the severity of these side effects seem to be dosedependent (5, 6).

In clinical trials, two cases of severe cutaneous adverse reactions have been described – one as “persistent and progressive rash” (4) the other as “exfoliative dermatitis” (8). Furthermore, acute generalized exanthematous pustulosis (9), erosive oral lichenoid reaction (10), Stevens-Johnson syndrome (11) and pityriasis rosea (12) have been reported in individual patients each treated with imatinib mesylate.

The clinical and histological features of the skin lesions that occurred in our patient two months after the onset of imatinib mesylate therapy for CML resemble those of pityriasis rosea. The patient was given no concurrent medication and had no history or evidence of any intercurrent infections. Based on clinical, histological and laboratory criteria the following dermatoses were excluded: seborrhoeic and discoid dermatitis, psoriasis, lichen planus, tinea corporis, secondary syphilis, cutaneous lupus erythematosus and T-cell lymphoma.

It is well known that pityriasis rosea may be atypical in its clinical course and morphology of cutaneous lesions. We therefore cannot definitely rule out the possibility that the eruption of our patient represented pityriasis rosea that transiently disappeared under methylprednisolone therapy and relapsed due to its withdrawal and not because of readministration of imatinib mesylate. However, this possibility seems unlikely in view of the lack of herald patch, central clearing and colarette of scale on the margin of the lesions, the absence of the “Christmas tree” pattern of distribution of the latter, their deterioration upon increase of imatinib mesylate dose and their resolution only under methylprednisolone therapy.

Eruptions similar to those described here are not uncommon under systemic treatment with a variety of pharmacological agents, including metronidazole, captopril, anti-inflammatory and antipyretic drugs (13 – 15). A world-wide and possibly long-term therapeutic application of imatinib mesylate in patients with CML is presently not available. It is therefore of interest to know that disseminated erythematous and pityriasisiform plaques represent a potential cutaneous side effect of this compound that may not require discontinuation of its administration.

REFERENCES