Imatinib causing drug rash with eosinophilia and systemic symptoms: A rare cutaneous reaction

Sir,

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by reciprocal translocation between the long arms of chromosomes 9 and 22 generating the Philadelphia chromosome, that leads to the formation of Bcr-Abl oncogene.[1] This encodes Bcr-Abl protein, leading to constitutive activation of the Abl tyrosine kinase. Imatinib mesylate, the first selective tyrosine kinase inhibitor (TKI) targeting Bcr-Abl protein, is effective in the treatment of CML by inducing complete remission and decreased mortality. Most common side effects of TKI include myelosuppression, nausea, vomiting, diarrhea, and skin rashes.[2] Herein we report a case CML who developed features of drug induced rash with eosinophilia and systemic symptoms (DRESS) on initiation of imatinib along with a review of literature regarding its frequency, confirmation of diagnosis and management issues.

A 53-year-old male diagnosed with CML in 2005 was treated with hydroxyurea only as he could not afford TKI. He was otherwise asymptomatic except for mild weakness. He had no residual organomegaly or lymphadenopathy. Complete blood counts (CBC) were unremarkable with normal total and differential leucocyte counts. In 2013, cytogenetic re-evaluation

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showed t (9;22) in 70% metaphase. He was started on imatinib mesylate 400 mg once daily. After taking the drug for 18 days, he developed a macular rash over his face associated with scaling and pruritus. The lesions progressed rapidly to involve the entire face with peri-orbital edema and swelling of lips [Figure 1]. He had a few lesions over the back; other of body surfaces not involved. There were no stigmata of insect bite. He had no previous history of allergy or any recent history of taking any other drug. There was no significant family history. On admission, his pulse rate was 122/min, blood pressure 88/50 mmHg and respiratory rate 24/min. Complete blood count showed a hemoglobin of 13.2 g/dl, total leucocyte count of 22.7 × 10^3/μl with neutrophils-48%, lymphocytes-12%, monocytes-6% and eosinophils-34%, and many atypical lymphocytes. The absolute eosiniphil count (AEC) was 7.4 × 10^3/μl. Liver and renal function parameters were normal. Imatinib was with-held and he responded well to oral prednisolone (1 mg/kg/day) along with parenteral hydration. AEC returned to normal (38 cells/cumm) by day 8, and prednisolone was tapered off. After two weeks, he was restarted on imatinib at a lower-dose of 200 mg/day. After three days, he again developed periorbital edema with itching over face along with peripheral blood eosinophilia. Imatinib was discontinued and oral prednisolone restarted. The patient responded with resolution of rash and eosinophilia in one week. After two weeks, he was restarted with low-dose imatinib along with oral steroids, which he tolerated well. At present, he is on prednisolone 5 mg daily and imatinib 200 mg/day with no adverse effect [Figure 2].

Imatinib is responsible for grade 1-2 skin rashes in 30-40% of the patients.[2] Although rare vasculitis and Stevens-Johnson syndrome has been reported in a few cases, skin rash associated with imatinib is generally mild and is most often characterized by maculo-papular lesions occurring prominently over the forearms, trunk, and occasionally, the face. Grade 3-4 rash was noted in 2-5% of patients in two studies.[2] Hair depigmentation and periorbital edema are two other cutaneous abnormalities associated with imatinib. DRESS has very rarely been reported with imatinib.

DRESS syndrome stands for drug reaction (or rash) with eosinophilia and systemic symptoms. The term was coined in a 1996 report for a syndrome recognized as early as 1959.[3] Recently, a scoring system, European registry of severe cutaneous adverse reaction (RegiSCAR) has been proposed for classifying DRESS syndrome.[4] RegiSCAR constitutes a SCAR, including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS. RegiSCAR's scoring system was designed to grade DRESS cases as "no", "possible", "probable", or "definite" case. The present case had RegiSCAR scoring of five (AEC >1500 cells/cumm, presence of atypical lymphocytes, typical skin rash, negative blood cultures, antinuclear antibody

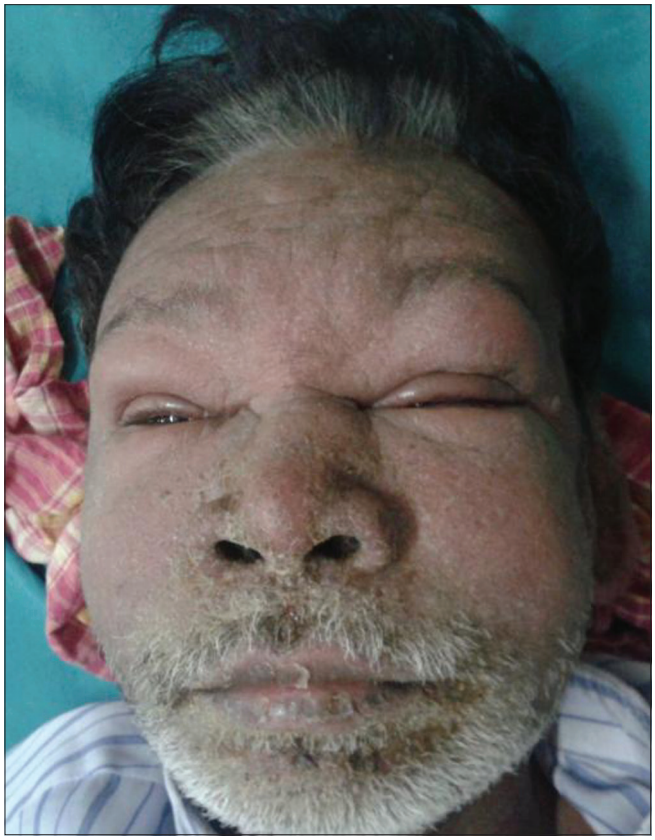

Figure 1: Patient at presentation

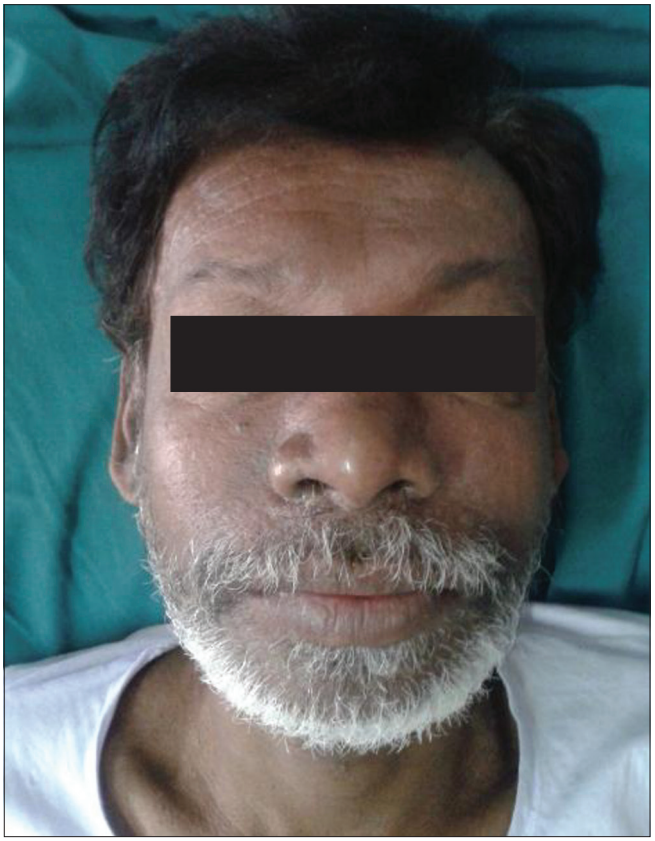

Figure 2: After therapy with oral corticosteroids

and vial serology), that made him a "probable" case as per the scoring system.

Although skin rash occurs quite often during treatment with TKI's, there is insufficient evidence-based data to establish guidelines on the management of DRESS. Due to their substantial clinical benefit, continuation of therapy is preferred while the skin rash and other side effects are aggressively managed. Topical preparations of antiseptics, antibiotics (e.g. 1% clindamycin) and steroids have been used.[5] Short-term systemic steroids are very useful, especially in patients with grade 3-4 rashes. Prednisone (30-50 mg/day) for 2 weeks offers good protection, then either gradually tapered off or kept on a maintenance dose of 5 mg/day for the duration of course of treatment, depending on the likelihood of recurrence of skin rash.[6] The present patient was unique as after initiation of lower-dose of imatinib, his symptoms of DRESS recurred. The patient responded only when lower-dose imatinib and prednisolone were given in combination.

In conclusion, although imatinib is associated with milder skin reactions in a few patients, but the presence of systemic symptoms along with eosinophilia should alert physicians to search for the possibility of DRESS, which could be life-threatening if not managed promptly.

Meet Kumar, Prakas Kumar Mandal, Tuphan K. Dolai, Maitreyee Bhattacharya

Department of Hematology, NRS Medical College, Kolkata, West Bengal, India

Address for correspondence:
Dr. Prakas Kumar Mandal,
8C/1/N, Roy Para Road, Kolkata - 700 050, West Bengal, India.
E-mail: prakas70@gmail.com

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