CASE REPORT

Imatinib-induced Stevens-Johnsons syndrome

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dr.himanshu.reddy@gmail.com**SUMMARY**

Imatinib mesylate is a tyrosine kinase inhibitor used widely as the first-line treatment for chronic myeloid leukaemia (CML). The side-effect profile of this drug includes fluid retention, muscle cramps, diarrhoea, myelosuppression and skin rashes. Of these, rashes of the type maculo-papular eruptions and oedema developed most commonly. The cutaneous adverse reactions other than maculo-papular eruptions are rare with imatinib. Severe and life-threatening cutaneous reactions can occur in 5% cases. Here, the author reports a case of newly diagnosed CML that developed Steven-Johnsons syndrome due to imatinib therapy. Patient responded and discharged successfully on withdrawal of the culminating drug.

BACKGROUND

Chronic myeloid leukaemia (CML) is a haematological malignancy with incidence of 1.5/100 000 people/year with higher incidence in men. Most patients present with fatigue, malaise, weight loss and pain in the abdomen. Minimal to moderate splenomegaly is the most common physical finding. Elevated leucocyte counts with increase in both immature and mature granulocytes were present at diagnosis. Different treatment modalities available are allogenic transplantation, drugs (imatinib, interferon- α and cytarabine), chemotherapy (hydroxyurea and busulphan), leukopheresis and splenectomy.

Imatinib mesylate is a tyrosine kinase inhibitor used widely as the first-line treatment for CML. It is more effective than interferon- α and cytarabine in newly diagnosed cases. The side effects of this drug are myelosuppression, fluid retention, muscle cramps, diarrhoea and skin rashes. A variety of adverse cutaneous reactions have been described with imatinib. Of these, rashes and oedema occur most commonly, the incidence being 66.7% and 65%, respectively.¹ The incidence of severe and life-threatening reactions occur in 5% cases.¹ Reports of cutaneous adverse reactions other than maculo-papular eruptions are rare with imatinib. However, it may cause acute generalised exanthematous pustulosis, oral lichenoid eruption,² vasculitis,³ epidermal necrolysis,⁴ hypopigmentation,⁵ erythema nodosum,⁶ exfoliative dermatitis⁷ and Stevens-Johnson syndrome (SJS).^{8–11}

SJS is a potentially deadly skin disease that usually results from a drug reaction. In most cases, these disorders are caused by a reaction to drugs like non-steroid anti-inflammatory drugs, allopurinol, phenytoin, carbamazepine, barbiturates, anticonvulsants and sulfa-antibiotics. The condition can sometimes—although not very often—be attributed

to a bacterial infection, and in some cases there is no known cause for the onset of SJS. However, the most common cause is through drug-related reaction. Here, the author describes a case of imatinib-induced SJS.

CASE PRESENTATION

A 51-year-old man had been diagnosed with CML in February 2012. He had no history of any chronic illness. There was no history of similar illness in the near relatives. The diagnosis of CML was made while he was being worked up for his complaints of dyspnoea on exertion for the past 1 year. Clinical examination, except mild pallor and splenomegaly, was normal. His initial total leucocyte count (TLC) was $1.23 \times 10^9/l$; bone marrow examination had features of CML; and reverse transcriptase PCR for BCR-ABL was 54.4% (kit method). He had been continued on imatinib therapy (400 mg/day) for 90 days. He developed skin rashes with severe itching all over the body in May 2012, which brought him to our hospital. Rashes were extremely itchy, starting from the trunk, and had encroached to the face and the genitalia. The patient was suspected to have drug (imatinib)-induced rashes. He stopped receiving imatinib therapy and was managed on supportive care. The patient thus improved (his skin rashes subsided). The patient was sent to the haematology department where again imatinib was started (200 mg/day since May 2012) after taking informed consent. This resulted in flaring of the skin lesions with appearance of vesicobullous lesions with few pustular lesions within 2 days. The diagnosis of SJS was considered. The lesions were severely itchy with exudation of pus with the involvement of mucous membranes (figure 1).

INVESTIGATIONS

Investigations showed TLC $3.2 \times 10^6/l$ (at start of therapy, it was $1.23 \times 10^9/l$). Blood cultures and pus culture were negative for the presence of any organism. The biopsy of the lesions was done, and it showed chronic dermatitis with reactive vasculitis (figure 2).

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of these rashes included some infectious aetiology, some allergic reactions or any drug reaction.

TREATMENT

The offending drug (imatinib) was withdrawn, and supportive treatment in the form of antihistaminics and calamine lotion for local application was given.

To cite: Jha P, D H, Jain N, et al. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007926

Figure 1 Vesicobullous lesions with pus exudates over the anterior chest wall of the patient.

OUTCOME AND FOLLOW-UP

Rashes started clearing within 3–5 days. The patient was discharged after 10 days of admission on the same treatment and was advised to attend the haematology outpatient clinic for follow-up of CML where he was put on dasatinib therapy (100 mg/day). In the last follow-up in October 2012, his TLC was $6.8 \times 10^6/l$ and the patient was doing well.

DISCUSSION

In this case, we investigated the patient and found that his blood cultures were sterile. The pus exudate from the eruptions was sent for culture and was found to be sterile. The patient had dramatic improvement when the drug imatinib was withdrawn. The itching and the rashes subsided. The lesions flared up again when the drug was started again in lower doses. This gives us the indirect evidence of SJS attributed to imatinib therapy. Of the five cases of SJS due to imatinib reported previously, three were males and two females. All these patients,

Figure 2 Biopsy of the skin lesion showed reactive vasculitis with inflammation around the vessels but not invading them.

except one, had CML.⁸ In two of these cases, the lesions reappeared on rechallenge with imatinib.^{11 12} In this case also, the patient's lesions subsided and then flared up when he was subjected to rechallenge with imatinib. The aetiology of SJS is not clear and drug-induced cases have been thought to be mediated by an immunological mechanism. Brouard and Saurat¹² have shown that the incidence of cutaneous reactions with imatinib increases with escalating doses of the drug. Valeyrie *et al*¹ have reported female sex and imatinib dosage as being independent risk factors for the development of rashes in a multivariate analysis.

Learning points

- ▶ This case highlights the life-threatening side effect in the form of Stevens-Johnson syndrome of the drug imatinib.
- ▶ The treating general physician should keep in mind this side effect when starting the drug imatinib for the treatment of chronic myeloid leukaemia.
- ▶ The appreciation of such cases is important because a mere stoppage of the culminating drug with supportive treatment could cause a reversal with dire consequences.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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