Spontaneous haemorrhage- Is imatinib the cause?

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ABSTRACT

Imatinib, a tyrosine kinase-C protein inhibitor remains the first choice for the management of chronic myeloid leukaemia (CML) since its introduction over a decade ago. Intracranial and gastrointestinal haemorrhages have been previously reported in association with Imatinib therapy. We report the case of a 47-yr-old man who was recently diagnosed with chronic phase of CML, that was complicated by a spontaneous intramuscular haematoma in the left gluteal region after 10 days of treatment with Imatinib. To the best of our knowledge, an intramuscular haemorrhage has not been described so far in association with Imatinib therapy. Clinicians should be alert to the possibility of spontaneous haemorrhage at unusual sites in patients being treated with Imatinib.

Keywords: Adverse events, complications, bleeding, tyrosine kinase-C inhibitor

INTRODUCTION

Imatinib (previously known as STI571) was formulated by rational drug design in the 1990s as target therapy for the treatment of CML. Following its success in the International Randomised Study of Interferon vs. STI571 (IRIS) trial, Imatinib emerged as the standard treatment for CML, and has since been used to manage several other malignancies, most notably gastrointestinal stromal tumours. Adverse reactions to Imatinib include cardiac abnormalities, abnormal bone and mineral metabolism, hepatotoxicity, and secondary malignancies among others. [1] Spontaneous haemorrhage has been reported during Imatinib therapy, usually in intracranial and intra-abdominal sites. [2, 3] We report the case of a 47-year-old man who developed a spontaneous intramuscular haemorrhage in the gluteal region whilst on low-dose Imatinib for CML, which resolved completely on withdrawal of the drug.

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CASE REPORT

A 47-year-old man from Southern India presented with progressive abdominal pain and distension. His physical examination revealed isolated massive splenomegaly without ascites. The haemoglobin level was 9.8 gm/l, white blood cell count 239,000/microlitre, and

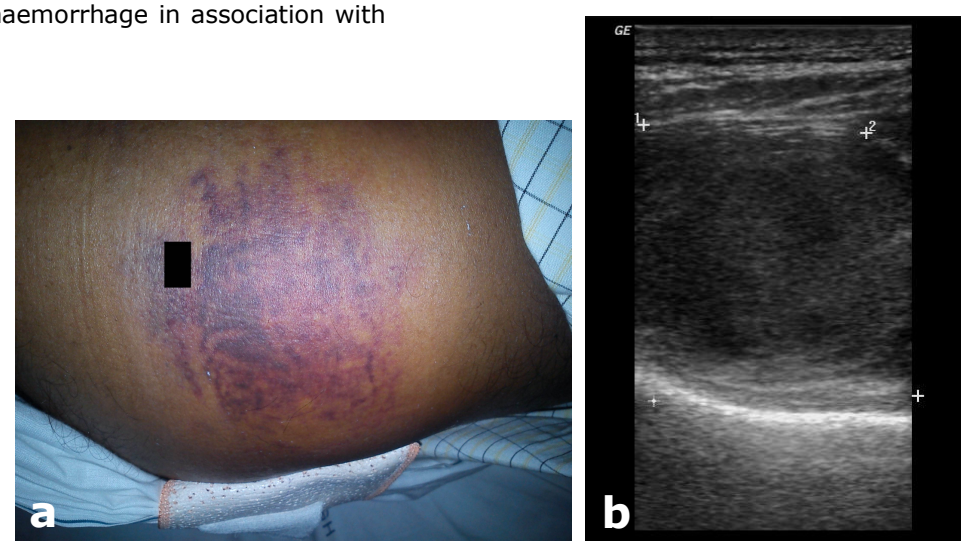
platelet count 279,000/microlitre. A peripheral blood smear showed chronic phase of CML, which was confirmed by a bone marrow biopsy. The prothrombin time was 14.2 sec (control 13.0 sec) and international normalised ratio (INR) was 1.12. There was evidence of concurrent active Hepatitis B virus infection as indicated by the surface antigen detected by chemiluminescence. Treatment was initiated with Imatinib 400mg and Lamivudine 100mg daily.

Ten days after starting therapy, the patient developed a spontaneous progressive painful swelling over the left gluteal region with overlying ecchymosis (Figure 1a). There was no prior history of trauma (bone marrow aspiration and biopsy was done earlier at the right posterior superior iliac spine), use of anticoagulants, or thrombocytopenia. Investigations at this time showed normal platelet count (253,000/mm^3) and INR. Ultrasonography of the swelling confirmed it to be in the intramuscular plane (Figure 1b). Altered blood was withdrawn from the swelling on needle aspiration of the swelling, confirming it to be a haemorrhage. Considering the possibility of spontaneous haemorrhage in association with Imatinib therapy, it was substituted with Hydroxyurea 500mg twice daily. The patient did not have any further episodes of bleeding, and the intramuscular haematoma had resolved completely (Figure 2) by the next fol-

DISCUSSION

The common side effects of Imatinib include nausea, vomiting, diarrhoea, periorbital oedema, fluid retention and myelosuppression. [1, 2] Central nervous system bleeding has been reported to occur in 5% of those in blast crisis, 1% in accelerated phase, and 0.6% in the chronic phase of CML when treated with Imatinib. [4] There is as yet no conclusive evidence that a high Imatinib trough level is associated with the development of major haemorrhagic events. One study by Song *et al*. showed that subdural haematomas developed at a median of 10 weeks (1-48 weeks) after start of therapy with Imatinib. [5] Our patient developed an intramuscular bleed 10 days after starting therapy at 400 mg daily.

The exact mechanism of spontaneous bleeding in patients treated with Imatinib is



Figs. 1: a) A painful swelling with overlying ecchymosis on the left gluteal region, and b) Ultrasonography scan of the swelling on left gluteal region of the patient showing an intramuscular lesion.

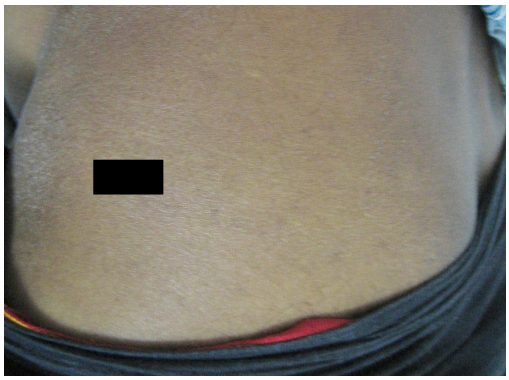


Fig. 2: The left gluteal region showing resolution of the swelling and ecchymosis after withdrawal of imatinib.

unknown. Thrombocytopaenia has been reported to occur in 16% of patients treated daily with over 200mg of Imatinib. [6] The platelet count and coagulation profile in our patient was normal at the time of presentation, and there was no history of any trauma or the use of anti-coagulants. Quintas has reported impaired Arachidonic acid-induced platelet aggregation in 10 out of 15 patients on Imatinib therapy. [7] Decreased levels of α2-plasmin inhibitor (α2-PI) has been demonstrated in patients with Philadelphia chromosome-positive lymphoblastic leukaemia, who developed haemorrhagic episodes while on treatment with daily 400 mg of Imatinib. [2] Interestingly, Shimabukuro-Vornhagen *et al.* reported improvement in platelet function in a patient with CML treated with Imatinib. [8] These authors felt that this may occur if the megakaryocytes also carried the BCR-ABL fusion gene.

The limitation of this report is that we were not able to perform platelet function studies, or assess the levels of α2-PI in our patient due to financial constraints. In our case, Imatinib seemed to be the likely aetiology since other causes of spontaneous haemorrhage have been eliminated. The possibility of interaction between Imatinib and Lamivudine also needs to be considered in our patient, and may require further study.

In conclusion, our case of spontaneous intramuscular haematoma highlights to clinicians the need to consider this possibility in patients treated with Imatinib. The exact mechanism of Imatinib-associated haemorrhage is unknown. Platelet function studies and estimation of α2-PI is indicated in such patients.

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