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Case Report

Imatinib induced bone marrow hypoplasia in a case of chronic myelogenous leukemia

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ABSTRACT

Imatinib mesylate a tyrosine kinase inhibitor first introduced for the treatment of chronic myelogenous leukaemia (CML) since May 2001, has revolutionised the management of CML. Imatinib is the first choice of treatment for patient with CML chronic phase (CML-CP) and generally the drug is well tolerated. A number of haematological and non-haematological side effects are associated with it. Bone marrow hypoplasia is one of the rare side effects noted with imatinib. We report a case of 46-year-old male a case of CML-CP who developed bone marrow hypoplasia following treatment with imatinib for a period of six months with bone marrow biopsy showing decreased cellularity.

Keywords: Bone Marrow, CML, Hypoplasia, Imatinib

INTRODUCTION

Chronic myelogenous leukaemia (CML) is myelopoliferative neoplasm characterised by abnormal proliferation of pluripotent stem cells. About, 90-95% cases of CML are associated with t (9; 22) which results in Philadelphia (Ph) chromosome.[1] This translocation fuses the sequences of Bcr gene on chromosome 22 to that of sequences of Abl-1 gene on chromosome 9 leading to formation of Bcr-Abl chimeric protein with increase tyrosine kinase activity.[2] BCR-ABL encodes a protein, P210BCR-ABL with dysregulated tyrosine kinase activity which is sufficient enough for leukemogenesis.[3] Imatinib mesylate is a tyrosine kinase inhibitor which binds to the ATP binding site of tyrosine kinase and keeps them in inactive form. Imatinib was first introduced in 2001 and was associated with significant improvement in cytogenetic response as well as complete haematological response as compared to low dose cytarabine and interferon alpha.[4] Imatinib became the gold standard for the treatment of CML for all phases. It is associated with various haematological and non-haematological toxicities that include anaemia, thrombocytopenia, nuetropenia, oedema, skin reactions, diarrhoea and nausea. Hypoplasia is a rare but serious toxicity that can be seen with imatinib. Here, we report a case of a 46-year-old male who developed bone marrow (BM) hypoplasia following imatinib therapy.

CASE REPORT

A 46-year-old male presented to our department in September 2017 with complaints of generalised weakness and abdominal distension. On examination he was found to have splenomegaly of 6cm below costal margin. He

was evaluated and complete blood count (CBC) was suggestive of (s/o) Haemoglobin (Hb) of 9.1g/dl, platelets of 250x109/l and total leukocyte count (TLC) of 151x109/l. Peripheral smear was s/o predominantly metamyelocytes and myelocytes with 3% of blast cells and 8% of basophills were present, hence a diagnosis of CML-chronic phase (CML-CP). Reverse Transcriptase polymerase chain reaction (RT-PCR) BCR-ABL was done which was s/o international standardised (IS) ratio of 45%. Thus, he was started on tablet (Tab) imatinib 400mg once a day. After 3 months patient was evaluated again and CBC was s/o complete haematological response (CHR) and RT-PCR BCR ABL IS ratio was 20%, in view of suboptimal response at 3 months, the imatinib dose was increased to 600 mg once a day. He reported back in February 2018 (i.e. at 6 months from diagnosis) with irregular treatment on imatinib with complaints of fever and fatigue. On evaluation, he had no splenomegaly or palpable nodes, CBC was s/o pancytopenia, with Hb being 5.4g/dl, TLC of 1100/l and Platelets being 6,000/l. Peripheral smear was s/o pancytopenia with no atypical cells. Bone marrow studies were suggestive of hypoplastic marrow with no atypical cells identified as shown in Figure 1 and Figure 2.

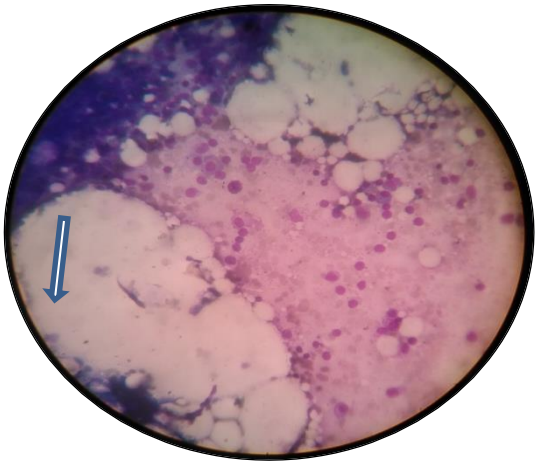

Figure 1: Bone marrow aspirate showing marrow spaces replaced by fat tissue.

RT-PCR BCR ABL IS ratio was 0.1% and imatinib resistant mutational analysis (IRMA) showed no mutation. He was managed with broad spectrum antibiotics and blood support, with febrile episodes being subsided. On repeated examination picture of pancytopenia was still present. Hence a diagnosis of imatinib induced bone marrow hypoplasia was made. In view of patient being stable even with low counts and considering good response to therapy but due to development of toxicity, patient was planned to start on low dose Nilotinib at 150mg/day. At present patient is on low dose Nilotinib with no complaints and the latest CBC is also s/o pancytopenia with Hb 5.2g/dl, TLC of 2000/l and platelets of 60,000/l. At present patient is on low dose Nilotinib and is tolerating well.

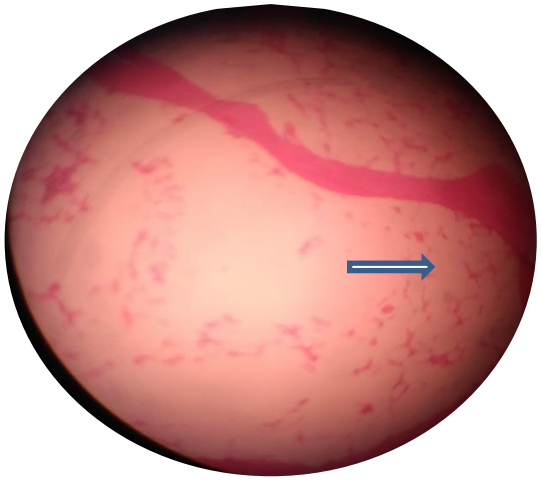

Figure 2: Bone marrow biopsy showing loss of cellularity of the marrow.

DISCUSSION

In an untreated case of CML, BM generally shows increased cellularity, with increased M:E ratio and increased blast and clustering fibrosis.[5] Post imatinib therapy there is decreased cellularity and decreased M:E ratio, blast and megakaryocytes.[5] Imatinib revolutionised the management of CML chronic phase with CHR and cytogenetic response ranging upto 95% and 85% respectively for newly diagnosed cases.[2] Generally, the drug is well tolerated with acceptable toxicity profile. Myelosupression is seen in patient receiving imatinib in the form of anaemia, thrombocytopenia and nuetropenia with anaemia being most common. Paul et al, in a retrospective analysis of BM biopsy sample of 683 patients of CML showed that 60 patients had grade ≥2 or more cytopenias out of which 18 patients had bicytopenia and 13 patients had pancytopenia.[6]

Bone marrow hypoplasia is a rare but serious side effect associated with imatinib therapy and can develop in any phase of CML. In the present case, patient developed BM hypoplasia following 6 six months of imatinib. There is limited data in literature regarding imatinib induced BM hypoplasia which is limited to case reports and case series. Srinivas et al, reported a series of five cases that developed bone marrow aplasia following therapy with imatinib, of these five cases, two developed aplasia in chronic phase, two in blast phase and one developed in accelerated phase.[7] Lokeshwar et al, reported a case of BM aplasia following 6 weeks therapy of imatinib who died because of mucormycosis.[8] The exact cause of BM hypoplasia in the present case or the above mentioned cases is not known. Possible reasons may be deficient BM stem cells or BM stromal damage due to previous therapies. Previous treatment with interferon alpha (IFN-α) has been associated with increased risk of hypoplasia. It is estimated that approx. 2% of CML patient treated with IFN-α will develop BM aplasia.[9] A correlation between the dose of imatinib and development of aplasia has also been attributed; with those treated with higher

dose develop hypoplasia much earlier.[7] Myelosupression during therapy has an adverse effect on overall response because therapy being withheld for myelosupression thus, decreasing the exposure to imatinib. Myelosupression has been identified as an independent adverse risk factor for achieving cytogenetic response.[10] In the present case patient achieved a complete cytogenetic response following 6 months of therapy with imatinib following which he developed hypoplasia.

CONCLUSION

Bone marrow hypoplasia is a rare but serious side effect associated with imatinib based therapy and should be kept in mind while patient is on therapy and is also an independent adverse factor in achieving response at molecular level. Regular hematologic follow up with blood counts and if necessary, bone marrow is required for patient management, so that drug can be withheld or dose can modified as per individual needs.

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