CASE REPORT

Central nervous system blast crisis of chronic myeloid leukaemia misdiagnosed as tubercular meningitis

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SUMMARY

Chronic Myeloid Leukaemia (CML) presenting with isolated Central Nervous System (CNS) blast crisis is an uncommon entity. A 22-year-old man, diagnosed with chronic phase CML in 2011 and was in haematological and cytogenetic remission until July 2016, had acute onset headache and vomiting with meningeal signs and was admitted elsewhere, investigated by brain imaging and cerebrospinal fluid (CSF) analysis and suspected to have tubercular meningitis, for which steroids and antitubercular medications were started. The patient's sensorium further deteriorated, and Ventriculoperitoneal shunt surgery was done for hydrocephalus by a neurosurgeon. After 2 months of the illness, he was admitted to our hospital with a persistent headache, vomiting and altered sensorium. CSF for cytospin confirmed myeloid blasts. He was still in haematological remission. So, a diagnosis of isolated CNS blast crisis was made. The patient was started on triple intrathecal chemotherapy and cranial radiotherapy. He had improvement with treatment and is still in remission.

BACKGROUND

Chronic myeloid leukaemia (CML) is a clonal malignancy, characterised by the presence of Philadelphia chromosome, which is formed due to a reciprocal translocation between the long arms of chromosomes 9 and 22.¹

Disease course of CML is triphasic with a chronic phase and accelerated phase, followed by blastic phase after 3–5 years. In cases of blastic transformation, blast cells are increased in the bone marrow and blood. However, few cases of CML develop extramedullary disease due to infiltration by blast cells.²

Extramedullary blast crisis usually involves lymph nodes, bone, gastrointestinal tract, skin and soft tissues. In rare situations, extramedullary blast crisis can affect the central nervous system (CNS).³

Isolated blast crisis involving the CNS without haematological relapse is a rare entity. It is clinically characterised by headache, seizures with signs of meningeal irritation and focal neurological deficits.⁴ These features may have a resemblance to chronic tubercular meningitis, and as tuberculosis is endemic in India, tubercular meningitis can be diagnosed as a primary disease. However, by the cerebrospinal fluid (CSF) cytospin, CNS blast disease can be diagnosed quickly.

Imatinib mesylate, used in the treatment of CML, has poor CNS penetration; hence, CNS may serve

as a reservoir site for CML. Therefore, patients on long-term imatinib therapy with haematological and cytogenetic remission may rarely present with CNS blast crisis.⁵

Herein, we report a patient of CML, who developed CNS blast crisis while receiving imatinib therapy, despite being in haematological and cytogenetic remission.

CASE PRESENTATION

A 22-year-old man, diagnosed with CML in 2011, was on imatinib 400 mg daily and had complete haematological and cytogenetic remission until July 2016. He developed fever, headache, nausea and vomiting and was admitted elsewhere, suspected of having tubercular meningitis by CSF analysis and MRI of the brain. He was started on antitubercular treatment along with steroids. Initially, for a few days, he had temporary relief from symptoms, but he gradually deteriorated for which right Medium Pressure Ventriculoperitoneal (MPVP) shunt was done in September 2016. Even then, he continued to experience headache, nausea, vomiting and gradual decline in sensorium and was admitted to our hospital, which is a tertiary care hospital in North-West India. On general physical examination, vital signs were normal. He had no organomegaly, and there was no evidence of skin or mucosal bleeding. On neurological examination, he was drowsy, had signs of meningeal irritation and bilateral papilloedema with restricted abduction in both eyes. A possibility of CNS blast crisis was considered.

INVESTIGATIONS

Investigations revealed haemoglobin 132 g/L (133–162 g/L), white cell count $5.40 \times 10^9/L$ ($3.54–9.06 \times 10^9/L$) and platelet count $168 \times 10^9/L$ ($165–415 \times 10^9/L$). Peripheral smear was normal with a differential count of 0.70 neutrophils, 0.25 lymphocytes, 0.02 eosinophils, 0.02 basophils and no atypical or blast cells. Lactate dehydrogenase was 9.44 $\mu\text{kat/L}$ (2–3.8 $\mu\text{kat/L}$). Serum electrolytes and liver and renal function tests were normal. CSF analysis revealed 75 cells (80% lymphocytes, 20% polymorphs), sugar 1.1 mmol/L (2.22–3.89 mmol/L) with corresponding blood sugar of 4.3 mmol/L and protein 3.40 g/L (0.15–0.50 g/L). CSF for malignant cytology was suggestive of CNS infiltration by immature myeloid cells including leucoblasts. Blast cells showed positivity on myeloperoxidase (MPO) staining, suggestive of myeloblasts (figure 1).

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Figure 1 Cerebrospinal fluid cytology: (A) shows blast cells characterised by rounded mononuclear immature cells with hyperchromatic nuclei; (B) myeloperoxidase stain shows myeloblasts.

Quantitative BCR-ABL1/ABL1 transcript ratio by reverse transcription-PCR was 2.538%. MRI of the brain was suggestive of ill-defined foci of altered signal intensity, hyperintense on T2/FLAIR (Fluid Attenuated Inversion Recovery) and DWI noted in the bilateral capsuloganglionic region, bilateral thalamus and bilateral periventricular region and postcontrast meningeal enhancement (figure 2). So, a diagnosis of CNS blast crisis was kept.

TREATMENT

Antitubercular treatment was stopped, and the patient was shifted to the hemato-oncology department. The patient was started on twice weekly triple intrathecal chemotherapy with methotrexate, cytosine arabinoside and hydrocortisone along with cranial radiotherapy.

OUTCOME AND FOLLOW-UP

The patient received eight cycles of intrathecal chemotherapy. The CSF became negative for blasts after 4 weeks, and he showed

full recovery after completion of therapy. Subsequently, he was put on imatinib 400 mg daily. He has remained in remission for 1 year at last follow-up and is free from extramedullary disease with a complete haematological and cytogenetic response.

DISCUSSION

CNS blast crisis clinically and radiologically resembles meningitis or encephalitis, symptoms of which are a headache, seizures, signs of meningeal irritation and focal neurological deficits with lymphoid or myeloid blast positivity on CSF examination. Molecular testing of CSF may detect BCR-ABL oncogene.⁶

Imatinib mesylate has a vital role in the treatment of Philadelphia chromosome-positive leukaemias through selective inhibition of the BCR/ABL tyrosine kinase. It is the treatment of choice for CML in the chronic phase especially for patients in whom allogeneic stem cell transplantation is not feasible.⁷

Imatinib is actively transported out of the CNS by P-glycoprotein, which is a membrane-bound transport protein, to reduce the bioavailability of imatinib in CSF. The concentration of imatinib in

Figure 2 (A) MRI of the brain suggestive of hyperintensity in the bilateral capsuloganglionic region, bilateral thalamus and bilateral periventricular region; (B) MRI of the brain showing postcontrast meningeal enhancement.

CSF has been found to be about 175 times lower than in plasma by Takayama *et al.*⁸ Therefore, in patients with CML treated with imatinib, CNS may act as a reservoir site for malignant cells.

Leptomeningeal disease has also been observed in patients with CML who are on second-generation tyrosine kinase inhibitors, for example, dasatinib while sustaining a haematological and molecular remission, which is unusual in the absence of ABL1 kinase mutations.⁹ Although dasatinib has good CNS penetration, CNS blast crisis may occur while receiving dasatinib due to an isolated clone containing a dasatinib-resistant mutation, which proliferated in this sanctuary site or inadequate effective drug concentration in the CSF.¹⁰

Our patient's initial presentation resembled that of meningitis with clinical features including headache, vomiting, altered mental status, signs of meningeal irritation and CSF picture of lymphocytic pleocytosis and raised proteins, which led to the previous misdiagnosis of tubercular meningitis. CSF cytology for malignant cells was not done previously. Although we have not confirmed the presence of the BCR-ABL oncogene in his

CSF, our patient had a significant amount of myeloid blasts in his CSF established on MPO staining and the presence of BCR-ABL oncogene was confirmed in his peripheral blood.

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REFERENCES

- Rowley JD. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973;243:290–3.
- Saikia TK, Dhabhar B, Iyer RS, *et al.* High incidence of meningeal leukemia in lymphoid blast crisis of chronic myelogenous leukemia. *Am J Hematol* 1993;43:10–13.
- Rajappa S, Uppin SG, Raghunadharao D, *et al.* Isolated central nervous system blast crisis in chronic myeloid leukemia. *Hematol Oncol* 2004;22:179–81.
- Hehlmann R. How I treat CML blast crisis. *Blood* 2012;120:737–47.
- Altintas A, Cil T, Kilinc I, *et al.* Central nervous system blastic crisis in chronic myeloid leukemia on imatinib mesylate therapy: a case report. *J Neurooncol* 2007;84:103–5.
- Jin GN, Zou P, Chen WX, *et al.* Fluorescent in situ hybridization diagnosis of extramedullary nodal blast crisis. *Diagn Cytopathol* 2013;41:253–6.
- Peggs K, Mackinnon S. Imatinib mesylate—the new gold standard for treatment of chronic myeloid leukemia. *N Engl J Med* 2003;348:1048–50.
- Takayama N, Sato N, O'Brien SG, *et al.* Imatinib mesylate has limited activity against the central nervous system involvement of Philadelphia chromosome-positive acute lymphoblastic leukaemia due to poor penetration into cerebrospinal fluid. *Br J Haematol* 2002;119:106–8.
- Gaur S, Torabi AR, Corral J. Isolated central nervous system relapse in two patients with BCR-ABL-positive acute leukemia while receiving a next-generation tyrosine kinase inhibitor. *In Vivo* 2014;28:1149–53.
- Al blooshi R, Vergidis D. Isolated CNS blast crisis of CML in a patient on dasatinib therapy. *J Leuk* 2016;4:212.

Learning points

- ▶ Patients with chronic myeloid leukaemia (CML), who are being treated with imatinib, may develop central nervous system (CNS) blast crisis despite being in haematological and cytogenetic remission.
- ▶ A high suspicion for CNS leukaemia should be thought in a patient with CML who presents with neurological complaints.
- ▶ Cerebrospinal fluid examination for atypical/blast cells by cytospin is essential in patients with CML who present with fever, headache, altered mental status and signs of meningeal irritation to be able to start appropriate treatment to prevent permanent neurological deficits.

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