CNS LEUKEMIC INFILTRATION IN CML PATIENT- A CASE REPORT

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ABSTRACT
Chronic myeloid leukemia (CML) is chronic myelo-proliferative disorder where there is reciprocal translocation of chromosomes 9 and 22 leading to formation of Philadelphia chromosome. Nowadays, the latest innovative management with Imatinib Mesylate which is a potent and selective inhibitor of Bcr-Abl and has action on both chronic and blastic phases of CML is recommended. Those patients who were on treatment with Imatinib Mesylate or the ones who had earlier achieved remission, secondary failures were observed in them especially in patients who were in blast crisis phase. A case has been reported in which a patient who had a complete cytogenic remission in the bone marrow but had unexpectedly experienced blast crisis of central nervous system (CNS) thus reflecting lower drug levels in CSF in comparison to plasma concentration.

Keywords: Chronic Myeloid Leukemia, Imatinib Mesylate, Blast Crisis, Central Nervous System

INTRODUCTION
CML is uncontrolled growth of the pluripotent hematopoietic stem cells. It has an initial chronic phase (CP), followed by an accelerated phase (AP) and a blast crisis (BC) as the disease progresses (Specchia et al., 1996). Lymph nodes, skin, soft tissues, serosal surfaces, bone, gastrointestinal and genitourinary tract are the common sites of extramedullary BC while CNS rarely gets involved (Alintas et al., 2007).
Imatinib Mesylate (IM) is a very effective treatment option in CML producing almost complete cytogenetic response in approximately 80-90% of CP patients (Rajappa et al., 2005; Bornhauser et al., 2004; Tsao et al., 2002; O’Brien et al., 2003). IM and its active metabolites show poor penetration across blood brain barrier resulting in it’s limited activity during CNS involvement (Alintas et al., 2007; Rajappa et al., 2005; Takayama et al., 2002).

CASES
A 33 year old gentleman, not a known case of diabetes or hypertension was diagnosed with chronic myeloid leukemia 7 months back. He was diagnosed to have CML in myeloid blast crisis and was treated with chemotherapy. He was in remission and search for allogenic transplant and where he matched unrelated donor (MUD). He had received one cycle of chemotherapy and had post HIDAC consolidation. The patient presented to hospital with chief complaint of altered sensorium for 1 day. On examination patient was in altered sensorium and was not obeying commands. The other higher mental functions could not be assessed however cardiac and respiratory examination were unremarkable. Per abdomen examination was soft and did not show any evidence of hepato-splenomegaly. On admission Hematological parameters revealed: Hb- 9.1gm%, Total WBC- 5000/UL, Myelocyte-2, Prometamyelocyte-2, N-84, L-12, B-0, E-0. Platelets count was within normal limits (1.8Lakhs). Biochemical parameters including liver and renal function tests were also normal. Special investigations included Bcr/Abl- 0%, CSF Malignant cytology – suggestive of leukemic infiltration (monocytoid cells were present). CSF cytology (Post TIT) after 2 week-clear.

Radiological Investigations
CT Head (On admission)- Multiple space occupying lesions in brain parenchyma.
MR Brain 1(plain + contrast) (On admission)- Multiple well defined enhancing leptomeningeal and dural based lesions scattered in brain parenchyma in keeping with leukemic infiltration.
MR Brain 2(plain + contrast) (after 3 weeks)- Interval decrease in size, enhancement and perilesional (increase the space).
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MR Brain 3 (plain + contrast) (after 10days) - Interval decrease in size, enhancement and perilesional edema of multiple well defined enhancing leptomeningeal and dural based lesions.

HRCT Chest- No structural lung parenchyma abnormality.

MR Brain 4(plain + contrast)- Interval decrease in size and number of lesions, (after 15days of last scan) with subtle enhancement and no significant perilesional edema noted.

Patient presented to us with altered sensorium and during the course in hospital, CT head was done which showed multiple space occupying lesions (SOLs) however, no definite evidence of intracranial hemorrhage was noted and so CEMR Brain was advised for further characterization of the space occupying lesions. CSF analysis was carried out as the brain biopsy was not feasible.

The patient was treated with 5 fractions of Triple Intrathecal Therapy (TIT) and 13 fractions of radiotherapy (RT) which were well tolerated. The patient’s sensorium improved significantly after receiving 3 fractions of RT and 1 cycle of TIT.

There was complaint of mild headache and fundoscopic examination was performed which did not reveal any evidence of papilledema. The patient was discharged and was called up for follow up after 10days with complete blood profile for sixth TIT and MRI Brain to look for temporal resolution of the lesions.

DISCUSSION

In the present case the patient was initially treated with Imatinib Mesylate following which remission was attained and bone marrow transplant was planned from a matched unrelated donor (MUD) but before that the patient presented in altered sensorium and was diagnosed with CNS leukemic infiltrates on CEMR. Subsequent MR studies showed residual metastatic lesions with significant interval decrease in size, number, enhancement and perilesional edema. Most malignant form of chronic myeloid leukemia is in blast crisis phase though it has morphological similarity to the de novo leukemia and it’s response to therapy has been found to be poor (Alintas et al., 2007). Extramedullary blast crisis have shown to
involve central nervous system in 14% of patients predominantly treated with hydroxyurea (Isobe et al., 2009).

Imatinib Mesylate is the treatment of choice for chronic myeloid leukemia particularly in chronic phase in patients whom allogenic stem cell transplant may not be possible. Imatinib Mesylate is a potent selective inhibitor which is being used for treatment of Ph+ leukemia (Narayan et al., 2011). Almost all patients with CML treated with Imatinib Mesylate therapy are successful in inducing prolonged remission however various animal models and humans studies have shown to have poor drug concentration in CNS (Kantarjian et al., 1992; Wolff et al., 2003; Petzer et al., 2002).

In patients who are diagnosed cases of chronic myeloid leukemia, CNS relapses or involvement has been noticed even after successful treatment with Imatinib Mesylate (Tsao et al., 2002). The patients usually present with headache and vomiting (Narayan et al., 2011; Kim et al., 2006; Thavaraj et al., 2008). CNS blast crisis have been reported in patients of CML who have attained complete or major cytogenic response in patients with imatinib (Bornhauser et al., 2004). Only few cases have been reported in Indian scenario with central nervous system involvement in patients already diagnosed case of CML and on treatment with IM.

![Imaging Results](image-url)

2. (a), (b), (c) and (d) Axial T2W Images Showing Progressive Decrease in Size and Surrounding Edema of the Representative Lesion in the Right Fronto-Temporal Region Following Treatment
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3: (a), (b), (c) and (d) Axial T1+C Images Showing Progressive Decrease in Size and Enhancement of the Representative Lesion in the Right Fronto-Temporal Region Following Treatment
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Conclusion
We conclude that the patient who is a known case of chronic myeloid leukemia can have CNS involvement in blast crisis phase even if he had achieved complete cytogenic remission in the bone marrow.

This reflects that the concentration of the drug in the CNS had multifold lower levels as compared to plasma concentration as already given in the literature so the risk of the CNS metastasis has to be kept in mind in patients who are in chronic phase of CML rather than intracranial hemorrhage as the only possible diagnosis and CEMR can be done for characterizing lesions if clinically indicated.

4: (a), (b), (c) and (d) Axial T2W Images Showing Progressive Decrease in Size and Surrounding Edema of the Representative Lesion in the Right Frontal Region in Parasagittal Location Following Treatment
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5: (a), (b), (c) and (d) Axial T1+C Images Showing Progressive Decrease in Size and Enhancement of the Representative Lesion in the Right Frontal Region in Parasagittal Location Following Treatment

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