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**CASE REPORT**

# CML with CNS infiltration: A case report

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**ABSTRACT**
We have described a known case of CML in chronic phase presenting with intracranial lesion and correlated neurological symptoms. Thus, it brings attention to the importance of thinking of CNS involvement in the presence of neurological symptoms in patients of CML, even in chronic phase. A comprehensive approach including both CSF study and neuroimaging, is needed for prompt diagnosis. So that early intervention can save the life of the patient.

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## INTRODUCTION

Chronic myeloid leukemia or chronic myelogenous leukemia is a hematopoietic stem cell (HSC) disorder.CML is characterized by translocation t(9;22) (q34;q11) resulting in the fusion of BCR-ABL fusion gene, with many subsequent effects on downstream pathways[1]. This translocation creates the BCR-ABL fusion gene, which encodes a consecutively active tyrosine kinase. This kinase activates various intracellular proteins, leading to uncontrolled cell proliferation. Treatment of CML has been of great success after introduction of Tyrosine kinase inhibitors (TKI), which targets BCR-ABL protein.CML is one of the model disease for targeted therapy. It is widely accepted that discovery of Tyrosine kinase inhibitors (TKI) has changed the treatment landscape of CML.

First- generation TKI, imatinib, induces complete hematologic, cytogenic and molecular remissions in 90%, 70% and 30% patients respectively.[2] Second-generation TKI, dasatinib and nilotinib, achieve higher and faster rates of cytogenic and molecular remissions in 90% and 70% patients respectively.[3,4]

Patients are monitored through complete blood counts and differential blood counts every two weeks until a complete hematological response is achieved. Molecular response are assessed by the ratio of BCR-ABL 1 to ABL 1 transcripts via quantitative PCR. Cytogenetic analysis is performed on bone marrow cells at the time of diagnosis and as when needed.While response rates in accelerated phase or blast crisis patients are generally lower, use of second generation TKIs are often associated with improved outcome. Some patients however fail to respond or relapse due to various mechanisms such as nonadherence, resistance example development of ATP binding pocket mutations in the BCR-ABL protein, expression of transporter proteins and epigenetic modifications[5,6].Clinician should be vigilant for treatment failure even after achieving therapeutic milestones and manage accordingly. Here, we report a case of isolated CNS involvement in an adult with CML-CP who was treated with dasatinib. The patient, was admitted owing to severe headache and visual disturbance. We highlight the importance of a CSF study in such patients with CML- chronic phase who present with common neurologic symptoms during TKI therapy.

## CASE REPORT

We present the case of a 36 year old male with known diagnosis of CML, came to the emergency with complaints of right sided headache for past 1 month which increased in intensity since past 10 days associated with projectile vomiting, decreased hearing and visual blurring since 2 days along with myalgia and fatigue.

Initial computed tomography (CT) of the head demonstrated a enhancing lesion in right petro-clival region with extension along posterior aspect of sphenoid body, correlating with the patient's symptoms.

Upon history review, the patient had been diagnosed with CML about 5 years prior to his presentation and had been started on imatinib 400mg but, due to concern for resistance against imatinib, the patient had



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been started on dasatinib 100mg but he developed right sided pleural effusion therefore dose was reduced to 50mg OD. The patient later lost follow up in oncology clinic.

Upon presentation, the patient's lab parameters were white blood cell (WBC)count of 5.22 cells/microL with shift to left and 0% blast, platelet count of 53,000/microL and hemoglobin of 12.1 g/dl.

Upon initial examination, the patient was alert and oriented. His pupils were mid dilated, reactive to light, right eye left rectus palsy, deep tendon reflexes were normal and motor and sensory examination was intact. His Fundus examination revealed Grade 2 disc oedema and Pure Tone Audiometry (PTA) showed Moderate mixed hearing loss on Right and Minimal hearing loss on left side.His Respiratory, GIT and CVS examination were normal. The peripheral smear showed normal counts with left shift. His differential cell count was Myelocytes 3, Metamyelocytes 2, Neutrophils and band forms 68, lymphocytes 21, Monocytes 10 and Eosinophils and basophils 0. Lumbar puncture was performed which showed an elevated opening pressure and increased CSF counts of 180 cells/cumm [myeloid series cells(90%) and shift to left with myelocyte, metamyelocyte and band forms along with 10% lymphomononuclear cells].Bone marrow aspiration showed a hypercellular marrow (>95% cellularity) with 8% blasts, having an immature immunophenotype. Aspirate was positive for the BCR-ABL oncogene when analyzed by FISH and PCR. BM biopsy showed features of CML in chronic phase.His Conventional cytogenetics yielded t(9;22) in all examined cells.BCR-ABL fusion signals were detected in 41% of cells.

Temporizing measures including steroid and mannitol were initiated due to the evidence of cerebral edema and mass effect. Dose of dasatinib was increased to 100mg daily. Neurosurgery consultation was taken and biopsy was planned but due to its venerable site it was deferred and they recommended serial repeat CT imaging. He was treated with total 30 Gy of radiation therapy delivered to whole brain for 10 consecutive days. With treatment his vomiting improved and intensity of headache decreased but visual symptoms persisted. Repeat imaging showed mild reduction in soft tissue component as compared to previous scan. Due to hemodynamic instability, patient developed acute worsening of mental status with Glasgow coma scale (GCS) of 6. He was intubated and started on ionotropic support. The patient became comatose and then expired because of metabolic acidosis with refractory hyperkalemia and refractory shock in the background of TLS, CML with CNS infiltration.

## DISCUSSION

CML, a clonal stem cell disorder, is characterised by fusion of BCR and ABL genes with constitutive overactivity of tyrosine kinase. CML runs a triphasic course, most patients being diagnosed in chronic phase, which evolves into blast phase within 4-5 years if untreated. CML is defined either by the presence of more than 20% blasts in the peripheral blood or bone marrow or by accumulation of blasts in the extramedullary sites like in 5-10% cases.[14] Although CNS involvement is atypical in CML, but it has been well-described.[8] Extramedullary blast crisis typically have a poor overall survival.

Normally males are more commonly affected than females at a ratio of 4.5:1 and the median age of diagnosis is 40 years. Isolated CNS symptoms in CML are rare. However when they occur, headache and vomiting are the most common presenting symptoms and should raise clinical suspicion of a CML relapse. On examination, papilledema is the most frequent finding observed during fundoscopy, while imaging typically reveals leptomeningeal enhancement[10].

In our case, the patient had persistent headache and vomiting, fundus examination revealed grade 2 papilledema and CSF showed myeloid precursors in the absence of systemic involvement. In CNS blast crisis, patients often present with clinical and radiological symptoms similar to those observed in meningitis or encephalitis. CSF testing typically reveals myeloid or lymphoblastoid cells and molecular analysis of CSF can sometimes identify the characteristics BCR-ABL oncogene. [9]

In this case CSF study revealed, increased cell count with slight shift to left and predominant myeloid cells. Any treatment decision regarding management of CML in blast crisis should include consideration of allogenic HSCT. The immunophenotype of the blasts should be assessed to determine if the cells are myeloid or lymphoid. Treatment should include a TKI with the specific choice dependent on prior therapy and mutation analysis. Treatment with TKI only may be a sufficient bridge to allogenic HSCT or it can be combined with conventional AML or ALL induction regimens for myeloid and lymphoid blast crises, respectively.Innovative strategies are urgently needed to treat these complex cases, such as high-dose Methotrexate or temozolomide. Thus, a meticulous selection of TKIs with enhanced blood-brain barrier permeability is crucial, coupled with systemic and CNS-directed therapy. Dasatinib, a second generation TKI, demonstrates superior potency in inhibiting the BCR-ABL oncogene compared with imatinib and plays a crucial role in managing CNS CML blast crisis, particularly when combined with whole-brain radiation therapy. [12,13] Most of the reported cases were treated with combined intrathecal chemotherapy (variable combination of methotrexate, cytarabine and dexamethasone) and craniospinal irradiation. Combined therapy was found superior to the intrathecal treatment alone in terms of treatment outcome.[15]In our patient, treatment regimen included dasatinib due to its proven ability to effectively penetrate the blood-brain barrier, in comparison to first-generation TKI imatinib along with whole brain radiation. Due to affordability issue intrathecal



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methotrexate and cytarabine was deferred.While CML generally presents indolently in most patients, blast crisis have a poor prognosis. Effective disease management is crucial and when feasible, proactive measures for allogenic stem cell transplantation (allo-SCT) should be considered.[7]In terms of prognosis, the most important factor is blast count >30% in the peripheral blood is associated with poorer prognosis[11]. Myeloid immunophenotype and the use of TKI therapy prior to blast crisis are associated with worst prognosis[18].The complications associated with the highest mortality risk in CML are leukocytosis, TLS and disseminated intravascular coagulation (DIC), with leukocytosis being associated with a mortality rate of up to 40%[1617]. Key factors for management of complications includes monitoring fluid balance and checking serum uric acid, electrolytes including potassium and phosphate and renal function due to possible TLS[17].

## CONCLUSION

Here we described a known case of CML in chronic phase presenting with intracranial lesion and correlated neurological symptoms. Thus, it brings attention to the importance of thinking of CNS involvement in the presence of neurological symptoms in patients of CML, even in chronic phase. A comprehensive approach including both CSF study and neuroimaging, is needed for prompt diagnosis. So that early intervention can save the life of the patient.

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