

Case Report

Isolated Central Nervous System blast crisis in chronic myeloid leukemia: A rare case report

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ABSTRACT

Chronic myeloid leukemia (CML) is a triphasic myeloproliferative neoplasm, characterized by the presence of the Philadelphia chromosome Ph+ (BCR-ABL fusion gene- t(9;22)), and most cases of CML manifest in the chronic phase with a high granulocyte count, while 5-10% progress to accelerated or blast crisis. Infiltration of the central nervous system as the only site of extramedullary blast crisis without bone marrow involvement is uncommon and deserves scrutiny. In such cases, a blast crisis could present with either myeloid or lymphoid infiltration, resulting in acute myeloid leukemia or acute lymphoid leukemia, respectively. Imatinib mesylate has promising activity in patients with Ph+ acute leukemias; however, its CNS penetration is poor. We report a 43-year-old male with CML-CP who developed isolated CNS blast crisis with an Early T-cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL) phenotype, and discuss the diagnostic and therapeutic approach.

Keywords: Bosutinib, CML, CNS blast Crisis, Dasatinib, ETP-ALL

INTRODUCTION

CML is a myeloproliferative disorder characterized by the reciprocal exchange of genetic material between chromosomes 9 and 22, resulting in the formation of the BCR-ABL gene- Philadelphia chromosome. This Philadelphia chromosome [t(9;22)(q34;q11)] arises when a segment of the ABL1 gene on chromosome 9 breaks off and attaches to the breakpoint cluster region (BCR) on chromosome 22.^[1] The BCR:ABL1 fusion gene encodes an oncogenic protein with constitutively active tyrosine kinase (TK) function, which drives unchecked proliferation of immature white blood cells and their accumulation in the blood and bone marrow.^[2] CML has been a triphasic disease, and the rate of progression from the chronic phase (CP) to the accelerated or blast phase (BP) has been mitigated to 1-1.5% from more than 20% after the introduction of tyrosine kinase inhibitors (TKIs).^[3] The extramedullary blast crisis can occur in 5-10% of patients; however, the incidence of the isolated central

nervous system (CNS) blast crisis without concomitant bone marrow involvement is uncommon. The blast crisis could be identified as either myeloid (60-80%) or lymphoid (20-30%), resulting in acute myeloblastic leukemia (AML) or acute lymphoblastic leukemia (ALL), respectively. Imatinib (the first signal transduction inhibitor (STI) introduced into clinical practice targets the BCR:ABL1 protein, thereby blocking its oncogenic signaling activity in CML, resulting in complete cytogenetic responses in more than 80% of cases. However, the CNS penetration of Imatinib is poor due to the P-glycoprotein-mediated efflux mechanism.^[4,5] Second-generation TKIs such as dasatinib, which also inhibits c-KIT and PDGFR, and bosutinib (SKI-606), an oral dual Src/Abl inhibitor with minimal PDGFR or c-KIT activity, exhibit distinct toxicity profiles due to their differential

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Received: 07 February 2025 Accepted: 30 September 2025 Published: 14 November 2025 DOI: 10.25259/ASJO_9_2025

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target selectivity. The introduction of TKIs has dramatically altered the natural history of CML, leading to markedly improved survival outcomes over the past decade.^[6] This report describes the case of a young man with CML-CP who developed an isolated CNS blast crisis after treatment with multiple lines of TKIs. The objective is to present this rare clinical scenario and highlight key diagnostic and therapeutic considerations.

CASE REPORT

A 43-year-old male presented with asymptomatic leukocytosis and was diagnosed with CML in October 2016. His Bone-marrow biopsy was suggestive of CML-CP with a high Sokal score (BCR-ABL transcript level by real-time polymerase chain reaction (RT-PCR): 4.102%) and based on that the treatment was initiated with Imatinib 400mg once daily (OD); the patient had a good cytogenic response in 6 months (BCR-ABL – 0.875%) and a deep molecular response in 12 months (BCR-ABL- 0.00%) so the treatment was continued subsequently. After 2 years of good drug compliance, in March 2019, there was a loss of molecular response where his BCR-ABL value rose to

3.2% and so the dose of Imatinib was escalated to 600mg OD. In December 2019, the BCR-ABL value was elevated to 47.94% and there was disease progression, so the patient

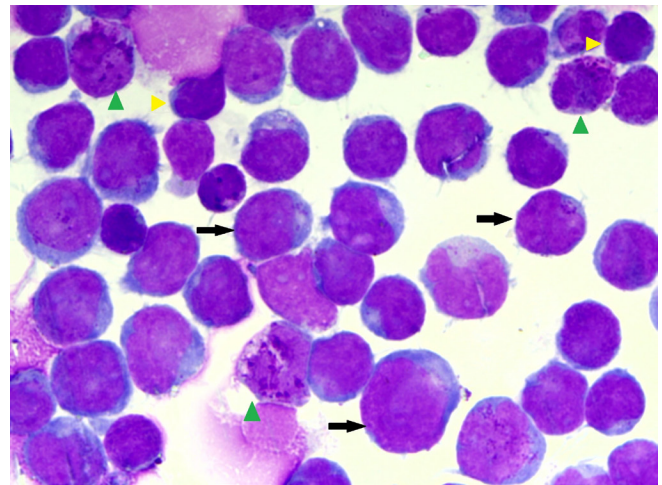


Figure 1: CSF cytospin smear (x1000, Leishman stain) shows numerous blasts (black arrows) along with few basophils (green arrow head) and few lymphocytes (yellow arrow head). CSF: Cerebrospinal fluid

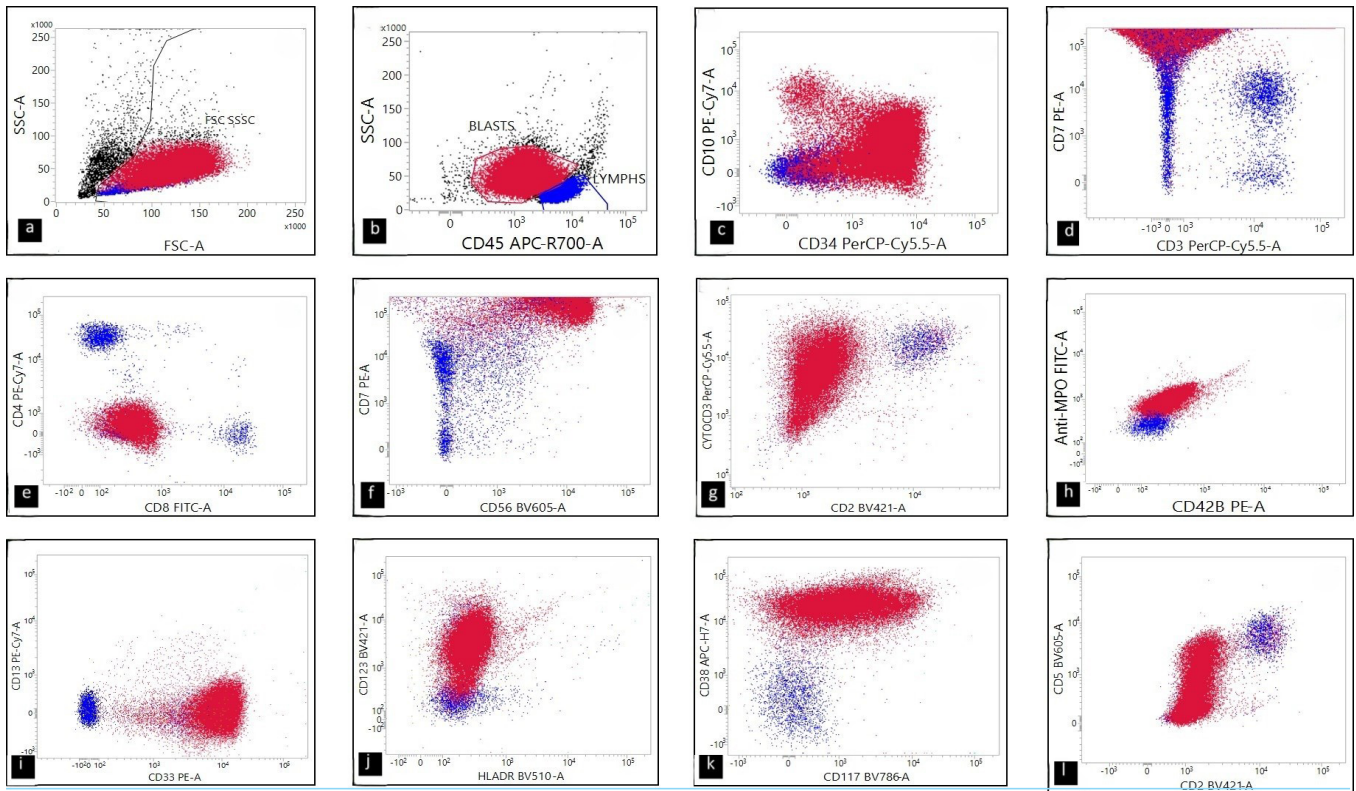


Figure 2: Flow cytometry analysis of the CSF shows (a-l) a population of blasts (red population) with (a) increased side scatter (SSC) and (b) forward scatter (FSC). (a-l) Few normal lymphocytes (blue population) are also seen. (b and c) The abnormal blasts express moderate CD45, moderate homogeneous CD34 in majority of blasts, with a small subset of blasts being positive for CD10 and negative for CD34. (d, f, g, i-l) Blasts are positive for CD7, cytoplasmic CD3, CD56, CD33, CSF: Cerebrospinal fluid CD117, CD123, and CD38. (e, g-j, l) Blasts are negative for CD4, CD8, CD2, CD42b, HLADR and MPO

was shifted to Dasatinib 50mg BD. The patient had a complete hematological response (BCR-ABL- 0.03%), and Dasatinib was continued for him. In March 2023, the patient complained of fatigue and breathlessness. His blood workup was normal; however, on examination, there was decreased air entry on the left side, and a chest x-ray revealed the presence of a moderate unilateral pleural effusion. Further investigations revealed negative cytology, normal ADA value, and negative for Koch's, suggestive of drug-induced pleural effusion. At this point, the patient was given a drug holiday for a week and was later shifted to Bosutinib 400mg OD. Within a week, he had episodes of disorientation with complaints of Nausea, vomiting, headache, and lethargy. His MRI brain was done, where periventricular and subcortical areas of ischemia were found. CSF examination showed sugar and protein levels of 28 mg/dl and 9.40mg/dl. CSF cytology smears [Figure 1] showed sheets of blasts, occasional mature lymphocytes, monocytes, and occasional RBCs, suggestive of blast crisis in this known case of CML. Flow cytometry of the CSF sample demonstrated a blast cell population (~84% of viable cells) with moderate CD45 expression and variable forward scatter. Immunophenotyping [Figure 2] revealed positivity for CD34; bright CD7; CD3, CD5, CD10 (small subset); CD33; CD117; CD123; CD56; and CD38; while negative for CD1a; CD2; CD4; CD8; CD42b; HLA-DR; and MPO. In view of the presence of more than one myeloid/stem cell marker (CD34, CD33, and CD117 seen in this case), bright CD7 with CD5 expression being one log dimmer than mature lymphocytes and absence of CD1a and CD8 overall features are suggestive of Early T-cell Precursor Acute Lymphoblastic Leukaemia (ETP ALL) CSF blast crisis in a known case of CML. Bone marrow examination confirmed and suggested an isolated CNS blast crisis in this known case of CML with normocellular bone marrow. Patient was treated with Bosutinib 400mg/day, weekly dose of vincristine, triple intrathecal therapy (methotrexate, cytarabine, and hydrocortisone) twice a week, and was later shifted to Hyper CVAD chemotherapy. Currently, he is symptom-free, tolerating the treatment, and doing well.

DISCUSSION

Central nervous system (CNS) blast crisis in chronic myeloid leukemia (CML) is exceedingly rare, particularly in the absence of bone marrow involvement. The present case describes an unusual isolated CNS blast crisis with an Early T-cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL) immunophenotype, following sequential tyrosine kinase inhibitor (TKI) therapy. This highlights the potential for sanctuary site relapse despite adequate systemic control, underscoring the importance of CSF cytology and flow cytometry in the timely diagnosis and management.

The blast crisis in CML is characterized by the type of cell involved (lymphoid or myeloid) and site of origin (medullary or extra medullary) and at least by one of the mentioned criteria – a) Presence of large-clusters of blast cells in bone marrow biopsy, b) >20% myeloblasts or lymphoblasts in the blood or marrow, c) Development of chloroma. CNS, lymph nodes, and bones are the commonest sites for extramedullary involvement by CML, where, in many of these patients, the bone marrow remains in CP.^[4] In a study reported by Alwan^[7], 21/53 CML patients were transformed to the acute phase, and later, 6/21 were transformed to ALL. The European Leukemia Network (ELN) had proposed in their 2006 guidelines that Imatinib 400mg/day be started as a first-line treatment in managing CML. Likewise, we initiated the treatment in our patient and also escalated the dose to achieve the target response. In 2009, ELN suggested a second-line treatment with Dasatinib or Nilotinib. In addition, allogeneic stem cell transplantation (ASCT) was recommended for blastic or accelerated-phase patients, and so we shifted the patient to Dasatinib to achieve the target response.

The CML-CP usually develops into accelerated or blast phase in 85% of patients, where approximately 50% develop a myeloid-BP, 25% have a lymphoid-BP, and 25% have an undifferentiated-BP.^[8] Almost 95% of lymphoid blast crises are of B-cell phenotype, whereas early T-cell precursor lymphoid blast crisis reflects a distinct subset of ALL with myeloid phenotype. The prevalence of Extramedullary blast crisis is extremely rare and is reported to be around 15% and most commonly involves bone, lymph nodes, soft tissue, and CNS.^[9] CML in blast crisis has shown to have a propensity for CNS involvement, and CNS relapses have been documented in 20% of patients with CML in blast crisis or Ph+ ALL already treated with imatinib.^[10] The possible pathogenesis of CNS leukemia is blood source diffusion, meningeal implantation, and cranial BM infiltration, and requires aggressive treatment, including ASCT. However, the CNS penetration of Imatinib is limited due to the increased efflux of the drug from the CNS due to P-glycoprotein, and CNS relapses have also been reported in CML patients receiving Imatinib after successful response. Dasatinib and Bosutinib have better CNS penetration and are effective in patients with relapses or who are at high risk of CNS disease.^[11] In the current study, the patient was on Dasatinib and still had progression in the CNS, and there is a dearth of such cases being reported. However, in the present case, flow cytometry was done, and the overall findings were most consistent with early T-cell precursor acute lymphoblastic leukemia (ETP-ALL), which is rarely documented. To our knowledge, this is only the second case to be reported as an extramedullary ETP-ALL blast crisis after the first one reported in 2020 by Wang *et al.*^[12]

Aggressive strategies like systemic and intrathecal chemotherapy, radiation, and ASCT are potential treatment modalities in CML with CNS blast crisis.^[13] In the present case, the treatment was initiated with a weekly dose of vincristine, Triple Intrathecal chemotherapy, and a second-generation tyrosine kinase inhibitor (Bosutinib). On stabilization of symptoms, the patient was started on Hyper-CVAD plus Bosutinib-based chemotherapy. The patient has tolerated the chemotherapy well and is symptom-free.

This case highlights an isolated CNS blast crisis in CML, a presentation rarely reported, as most cases involve simultaneous marrow disease. Unlike previous reports, the leukemic clone demonstrated an Early T-cell Precursor ALL (ETP-ALL) immunophenotype, which is scarcely described in CML blast crises. Comprehensive evaluation with cerebrospinal fluid cytology and flow cytometry allowed precise diagnosis, and sequential use of multiple TKIs illustrates the therapeutic challenges in managing isolated CNS disease. These features distinguish this case from prior reports and provide practical insights into diagnosis and treatment. As a single-patient report, the findings are not generalizable. Limited follow-up restricts assessment of long-term response and outcomes, and the absence of comparative data prevents definitive conclusions regarding optimal management strategies.

CONCLUSION

Isolated CNS blast crisis can occur in CML-CP patients receiving Imatinib or next-generation TKIs, even after achieving complete molecular and cytogenetic responses. Prompt cerebrospinal fluid evaluation, including cytology and flow cytometry, is essential for identifying rare subtypes such as ETP-ALL, facilitating accurate diagnosis and timely initiation of targeted therapy. Clinically, this underscores the need for vigilance in patients with neurological symptoms despite systemic remission and highlights the importance of integrating CNS-directed monitoring into management strategies. Given the rarity of this presentation, systematic reporting and further studies are warranted to better characterize risk factors, optimize therapeutic approaches, and improve outcomes in this subset of patients.

Author contributions: UM: Manuscript review and edit; DM: Manuscript writing and data collection; VM: Proof reading and manuscript finalization; KS: Data analysis and manuscript finalization; MR: Data analysis and data collection; VK: Manuscript edit and data analysis.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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How to cite this article: Maheshwari U, Morzaria D, Maniar V, Sehgal K, Ray M, Kaul V. Isolated CNS blast crisis in chronic myeloid leukemia: A rare case report. *Asian J Oncol.* 2025;11:19. doi: 10.25259/ASJO_9_2025