

## Case Report

# A Unique Case of Chronic Myeloid Leukemia Relapsing as an Isolated Blast Phase in the CNS and Literature Review

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Chronic myeloid leukemia (CML) is one of the most common hematologic malignancies characterized by the Philadelphia chromosome and pathogenic fusion protein BCR-ABL1. CML is considered a treatable malignancy with a favorable outcome. However, one of the familiar and often fatal sequelae of this disease, is when the chronic phase leukemia evolves into the blast phase in the peripheral blood or bone marrow, or in extramedullary proliferation of blasts with myeloid or less commonly lymphoid differentiation. Extramedullary blast phase of CML is a rare phenomenon. Here, we report a case of a patient with CML, BCR-ABL1-positive, who had achieved hematologic and cytogenetic remission, who presented with neurological symptoms including dizziness, weakness, and headache. An MR of the brain showed diffuse cerebral and cerebellar leptomeningeal enhancement, and small regions of parenchymal enhancement in the left frontal lobe. A brain biopsy of an area of leptomeningeal enhancement showed a leptomeningeal infiltrate of blasts and immature myeloid cells, weakly positive for myeloid markers such as myeloperoxidase, CD117 and CD68, and was negative for CD3, PAX-5 and CD20. Fluorescent in-situ hybridization performed using dual fusion was positive for BCR-ABL1 translocation in the leptomeningeal infiltrate, indicative of a t(9;22) involving these two genes. The patient is being treated with intrathecal chemotherapy at the time of this report. This case documents an unusual presentation of known sequelae of CML. Awareness of this phenomenon will help us diagnose and manage this complication in the future.

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**Key Words:** Chronic myeloid leukemia, Blast crisis, Acute leukemia, Blood cancer, Malignancy

## INTRODUCTION

Chronic myeloid leukemia (CML) is one of the most common hematopoietic neoplasms worldwide.<sup>1</sup> CML is a myeloproliferative neoplasm characterized by the presence of a reciprocal translocation between chromosomes 9 and 22, known as the Philadelphia chromosome that results in the expression of the oncoprotein, BCR-ABL.<sup>1-3</sup> Most patients with CML present at an early stage of the disease known as chronic phase (CML-CP). Despite the development of targeted therapy that has revolutionized the treatment of CML, a subset of patients progresses to the stage called blast crisis or blast phase (BP), a highly aggressive, often fatal stage of CML.

CML-BP presents a therapeutic challenge, as most patients typically exhibit a poor response to standard treatments of CML and have a poor outcome. Even though CML-BP mimics and acts as acute leukemia, it is not characterized as one. In

fact, acute myelogenous leukemia (AML) with BCR-ABL positivity is a distinct entity from the CML-BP. Many features have been enumerated in the current international consensus classification (ICC) and WHO classification that characterizes CML-BP.<sup>4,5</sup> Some of the principal features indicating the transformation of disease to CML-BP includes presence of 20% or more blasts in peripheral blood or bone marrow (BM), a large focus of blasts in BM, or proliferation of blasts in any extramedullary site.<sup>4,5</sup> Amongst the extramedullary sites, the central nervous system (CNS) as an isolated site of extramedullary blast involvement is extremely rare.

CNS is one of the most common extramedullary sites involved in acute leukemia.<sup>6,7</sup> CNS involvement leads to a wide range of neurological symptoms including headache, vomiting, seizure, and symptoms related to cranial nerve or peripheral nerve palsy. The underlying mechanism of CNS involvement entails the ability of the leukemic cells to cross the blood brain barrier. Infiltration of CNS, both the brain and spinal cord,

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requires different strategies of treatment, usually by intrathecal administration of chemotherapy. Since the involvement of CNS in CML-BP is extremely rare, the optimal treatment in this scenario remains controversial.<sup>8-14</sup>

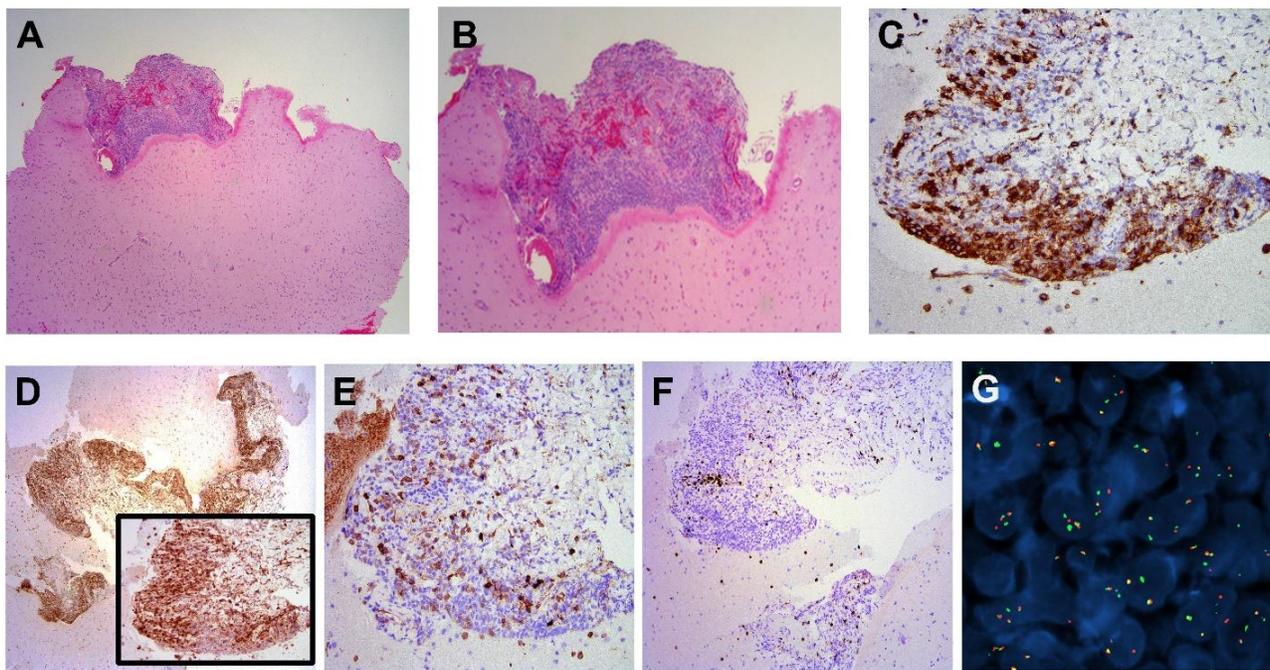
Here, we report a case of a patient with CML, BCR-ABL1-positive, who after achieving hematologic and cytogenetic remission, developed neurological symptoms. Upon further investigation, it was revealed that the patient had developed CNS involvement.

### CASE REPORT

A 57-year-old man with history of CML presented to the clinic with neurological symptoms of dizziness, weakness, and headache. He was diagnosed with CML three years ago when a routine peripheral blood count showed basophilia, neutrophilia, and thrombocytosis. The patient was put on

imatinib therapy and subsequently reached hematological and molecular remission. Upon presenting with neurological symptoms, an MRI was performed which showed diffuse cerebral and cerebellar leptomeningeal enhancements. Also, a small region of parenchymal enhancement was observed in the left frontal lobe. Interestingly, peripheral blood values were within normal range showing no abnormal myeloid blasts or progenitors.

A brain biopsy was performed from the area of the leptomeningeal enhancement that showed immature cells, possibly blasts, infiltrating the leptomeninges. Immunohistochemical stains showed the infiltrating cells to be positive for myeloperoxidase, CD117, CD68, and CD34 and negative for lymphoid markers including CD3, CD20, and Pax5. A fluorescent in-situ hybridization performed on these blasts showed positive result for *BCR-ABL1* fusion (**Figure 1**).



**Figure 1.** Histological features of the leptomeningeal mass. (A, B) Photomicrograph showing brain parenchyma being invaded by a haemorrhagic mass formed by immature blasts (H&E, 40X, 200X), (C-F) Immunohistochemical stain showing blasts are positive for (C) CD34 (100X), (D) CD68(40X, inset 200X), (E) CD117 (200X), and negative for (F) CD3 (40X). (G) Dual probe FISH showing fusion between *BCR1* (green) and *ABL* (red) genes in the blasts identified in the leptomeningeal mass.

These morphological and immunohistochemical findings indicated that the patient had blast phase (BP) transformation of the previously diagnosed CML. The patient's peripheral blood values were within normal range showing no evidence of increased blast count. Since most BP transformation of CML involves the peripheral circulation and bone marrow, a bone marrow biopsy was performed which demonstrated no indication involvement by acute leukemia. PET scan showed

no other possible tissue involvement. These findings indicated that the patient's CML blast phase was only limited to his CNS involvement.

The patient was subsequently treated with intrathecal methotrexate and cytarabine. At the time of this report (15 months after presentation with CNS blast crisis), the patient is disease-free.

**Table 1.** Clinical and pathological features of all cases reported in English literature documenting isolated CNS involvement by CML-BP.

Age at diagnosis (yr)	Age at presentation with isolated CML-BP in CNS (yr)	Relapse - free period (months)	Sex	Type of relapse (Myeloid vs Lymphoid)	Treatment before relapse	Treatment after relapse	Outcome	Reference	Year published
19	19	1.5	M	Lymphoid	HU + Imatinib + prophylactic IT CT	IT CT + RT+ imatinib	DOD	Pfeifer et al. (18)	2003
68	68	4	M	Lymphoid	HU+Imatinib	IT CT + RT	DOD	Pfeifer et al. (18)	2003
45	45	6	M	Lymphoid	HU, interferon, VCR + Pred + imatinib	IT CT + RT + imatinib	AWD	Pfeifer et al. (18)	2003
39	41	22	M	NA	Imatinib	IT Mx, C, Hy+ RT + imatinib	NED	Rajappa et al. (19)	2004
48	48	3	M	Myeloid	HU + imatinib + C + idarubicin	IT Mx, C + RT+ imatinib +C +	NED	Rytting et al. (20)	2004
46	48	26	F	NA	HU and interferon for 2 years followed by imatinib for 2 months	IT CT + RT + systemic CT	DOD	Beyazit et al. (21)	2005
50	52	14	M	Lymphoid	interferon for 2 months +imatinib for 1 yr	IT Mx, C, Hy + CT for ALL protocol followed by ALLSCT	DOD	Johnson et al.(22)	2005
42	44	25	M	Lymphoid	Imatinib	craniotomy, IT Mx, C, Hy+ Imatinib	DOD	Kim et al. (23)	2006
68	70	24	M	Lymphoid	imatinib	IT Mx, D + dasatinib + RT	Died of other disease	Barlow et al. (24)	2008
23	25	22	M	NA	Imatinib followed by BMT	IT CT + RT	NED	Oshima et al. (25)	2008
31	31	4	M	NA	Imatinib followed by BMT	IT CT + RT	Systemic replace after 1 month	Oshima et al. (25)	2008
61	63	14	M	Lymphoid	Imatinib	IT Mx, D, + imatinib followed by PBSCT	AWD	Isobe et al. (26)	2009
39	42	36	M	Lymphoid	Imatinib	IT Mx, C +imatinib	NED	Lee et al. (27)	2009
33	35	13	M	Myeloid	HU + imatinib, followed by SCT and dasatinib	IT Mx + RT+ nilotinib	NED	Thomas et al. (28)	2010
25	36	132	NA	NA	Allo-SCT, followed by three bone marrow relapses in 11 years, two treated by DLI and one by high dose imatinib	IT Mx, C, D + CD-14 depleted DLI +Nilotinib	DOD (after 17 months)	Neumann et al. (29)	2011
15	19	48	F	Lymphoid	imatinib	imatinib, IT CT, RT	LOF	Radhika et al. (30)	2011
37	41	48	M	Lymphoid	imatinib	imatinib, IT CT, RT	DOD	Radhika et al. (30)	2011
64	67	15	F	Myeloid	imatinib and dasatinib followed by HSCT	Shunt surgery, IT Mx, C, D+dasatinib	NED	Fuchs et al. (31)	2012
24	24	3	F	Myeloid	HU + imatinib	IT C, Hy+ dasatinib	NED	Lindhorst et al. (32)	2013
22	24	29	M	Lymphoid	Imatinib	IT CT, RT followed by SCT and dasatinib	NED	Nishimoto et al. (33)	2013
54	54	7	M	Lymphoid	Imatinib	IT Mx + RT +dasatinib	NED	Park et al.(34)	2014
30	37	84	M	Myeloid	imatinib/Nilotinib for 7 years, dasatinib for 6 months, ponatinib for 4 months	IT C + RT+ dasatinib	NED	Gaur et al. (35)	2014
33	38	60	M	NA	imatinib	IT Mx, C, D +Dasatinib	NED	Gomez et al. (36)	2015
32	33	9	M	Lymphoid	Dasatinib	IT MX, C, Hy + Allo-SCT	NED	Al blooshi et al.(37)	2016
35	37	25	M	Myeloid	Imatinib	Imatinib+ IT Mx, D	DOD	Jain et al.(38)	2016
5	5	8	M	Lymphoid	Imatinib	CT	NED	Jin et al. (39)	2018
14	15	14	M	Lymphoid	Imatinib	IT CT, RT	NED	Chatterjee et al.(40)	2019
57	58	8	F	Myeloid	Imatinib Dasatinib	IT Mx + RT + Dasatinib	DED	Bin Salman et al. (41)	2020
68	70	20	M	Myeloid	Imatinib	IT Mx + RT	DED	Arumugam et al. (42)	2020
22	27	62	M	Myeloid	Imatinib Nilotinib	IT Mx + Dasatinib	LOF	Arumugam et al. (42)	2020
12	13	12	F	L	Imatinib	IT CT + dasatinib	NED	Boudiaf et al. (43)	2020
8	9	14	F	L	Dasatinib	IT Mx, C, HY + HST	NED	Jo et al. (44)	2023

## DISCUSSION

In this case report, we present an intriguing instance of CML-BP occurring exclusively within the CNS of a patient. BP, characterized by the rapid proliferation of immature myeloid blast cells, is a severe manifestation of CML that typically involves the bone marrow and peripheral blood. However, the exclusive involvement of CNS in blast crisis is an exceptionally uncommon phenomenon, making this case noteworthy for its distinct presentation and diagnostic challenges.

Since the inception of tyrosine kinase inhibitor (TKI)-based therapy, the progression-free and overall outcome of CML has dramatically improved. However, the effectiveness of TKI in treating CML involving the CNS is not clear. The first line TKI agent imatinib was found in cerebrospinal fluid (CSF) as a low, subtherapeutic level.<sup>15-17</sup> This may explain why our patient remained disease-free in peripheral blood and bone marrow while suffering from a recurrence in the CNS. The other next generation of TKI agents such as dasatinib showed substantially better CNS penetrance and efficacy in treating CNS disease.<sup>14</sup>

A literature search was performed on PubMed and Google scholar to compile all the clinical and pathological details of all cases reported in English literature documenting isolated CNS involvement in CML-BP (**Table 1**).

The mechanisms triggering isolated CNS blast crisis remain poorly understood. Possible explanations may include a specific microenvironment within the CNS that allows and promotes the proliferation of blast cells. There may also exist specific genetic and molecular factors that enable blast cells to selectively infiltrate the CNS. Further research is necessary to explore these possible mechanisms and develop targeted therapeutic strategies.

Our case underscores the importance of considering atypical disease presentations in the follow up of CML patients. Isolated blast crisis involving the CNS necessitates a comprehensive diagnostic workup, including CSF analysis and neuroimaging. Clinicians should remain vigilant for neurological symptoms in CML patients even in the phase of hematological and molecular remission, as early diagnosis and management are essential for improving patient outcomes. Collaborative efforts between oncology and neurology teams are crucial to address the complex clinical and therapeutic aspects of isolated CNS blast crisis. As targeted therapies for CML continue to evolve, future research may provide insights into personalized treatment approaches for these rare and intriguing presentations.

## CONFLICT OF INTEREST DISCLOSURES

The authors have no conflict of interest to disclose.

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