


# Isolated Central Nervous System Infiltrated and Progressed to Acute Myeloid Leukemia from Chronic Myeloid Leukemia with e1a3 BCR-ABL1 Transcript: A Rare Case Report and Literature Review

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**Abstract:** The chronic myeloid leukemia (CML) is easily diagnosed by laboratory examination, however, rare BCR-ABL1 mRNA transcripts variants, such as e1a3 present diagnosis and therapeutic challenges. This case report details the diagnosis and management of a CML patient with the e1a3 transcript by FISH and RT-PCR. Following initial diagnosis, the patient was treated with the tyrosine kinase inhibitor (TKI) Flumatinib. During the treatment, although the FCM-MRD of the bone marrow kept negative, the e1a3 expression detected by PCR always remained positive. After eighteen months, the patient experienced headaches, vomiting, and blurred vision. Subsequent bone marrow analysis and flow cytometry detection of cerebrospinal fluid indicated that the patient had entered the blast phase, progressing to acute myeloid leukemia (AML). Treatment was switched to the third-generation TKI olverembatinib, combined with chemotherapy, followed by allogeneic hematopoietic stem cell transplantation. The patient remains disease-free following olverembatinib maintenance therapy. This case underscores the importance of comprehensive diagnostic approaches and the potential efficacy of third-generation TKIs and allo-HSCT in the treatment of e1a3-type CML.

**Keywords:** CML-BC, e1a3 transcript, CNS, HSCT, olverembatinib

## Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative characterized by the presence of the Philadelphia chromosome, arising from a t(9;22)(q34;q11) chromosomal translocation. This translocation results in the formation of the *BCR::ABL1* fusion gene, which encodes a constitutively active tyrosine kinase that drives the leukemic process.<sup>1</sup> Variations in the breakpoints within the BCR or ABL1 genes lead to diverse *BCR::ABL1* mRNA transcripts, with the e1a2, e13a2, e14a2, and e19a2 being the most common. Less frequent variants, including e1a3, e13a3, and e6a2, have been identified.<sup>2-4</sup> About 1% of patients with CML may have e1a2/a3 transcripts coding for the oncogenic protein P190, and these patients may have a worse prognosis.<sup>5,6</sup> e1a3 is a rare but poor prognostic transcript, as shown in several cases.<sup>7</sup>

CML has been widely characterized as a triphasic disease, progressing from a chronic phase through an accelerated phase to a blastic phase (BP). BP-CML a poor-prognosis acute leukemia, which may be myeloid, lymphoid, or mixed phenotype.<sup>8</sup> In addition to presenting with de novo BP-CML, patients may experience deterioration during therapy. CML can also progress towards the extramedullary blast phase due to the infiltration of blast cells, which can affect various parts of the body, including the bones, lymph nodes, gastrointestinal tract, skin, central nervous system (CNS), and soft tissues.<sup>9-11</sup>

Cases of CML invading the CNS are not rare,<sup>12-17</sup> the CNS progression of e1a3 subtype CML, especially isolated CNS infiltration without any relapse in the hematological aspects has not been reported. The present case report describes

a rare case of CML with the e1a3 BCR-ABL1 transcript, which is unique as it involves the emergence of an isolated CNS blast crisis during flumatinib maintenance therapy, despite achieving hematological and cytogenetic responses.

## Case Presentation

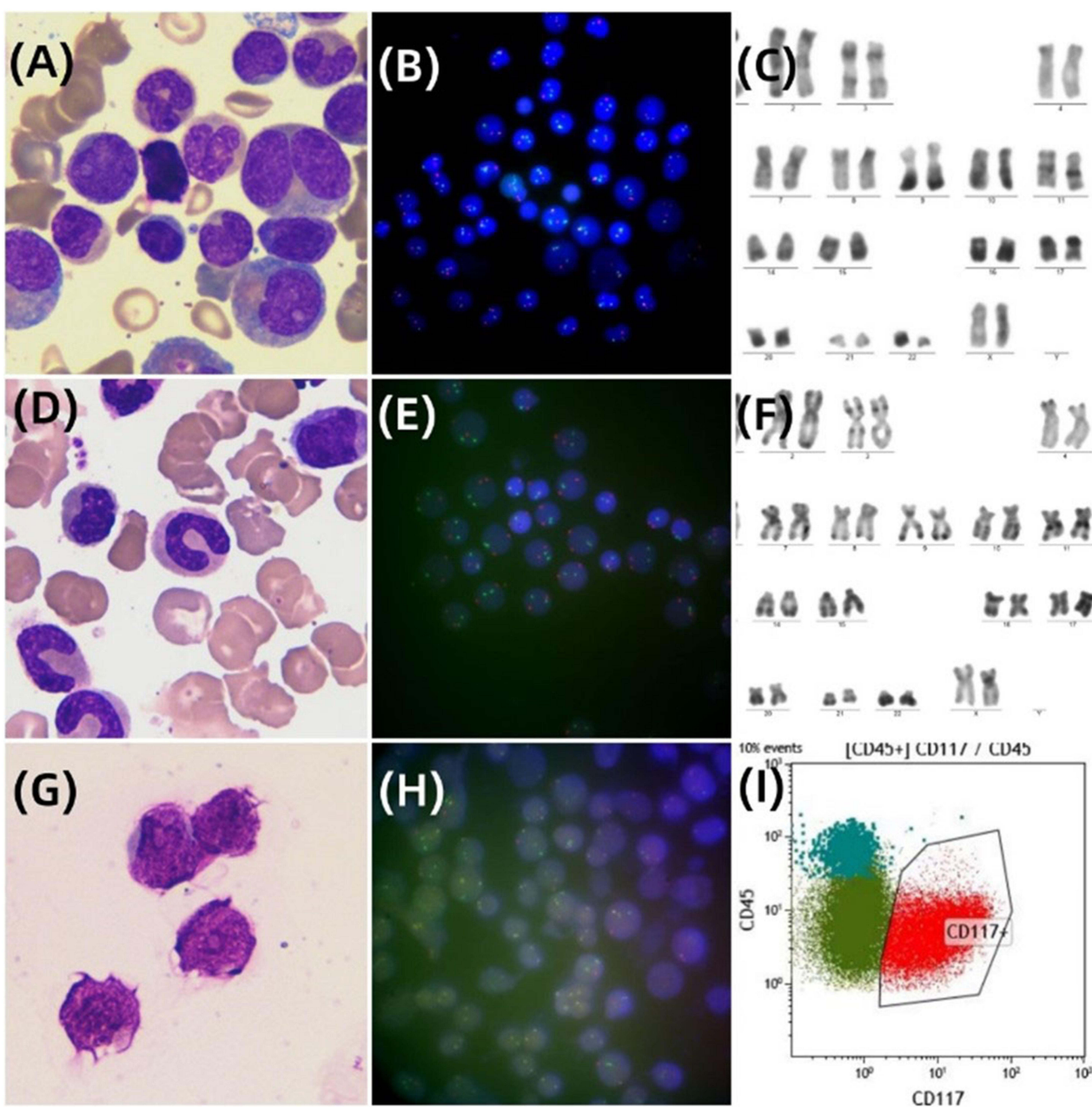
A 56-year-old Chinese female patient visited our center with the primary complaint of a high white blood cell (WBC) count discovered during a physical examination in June 2021. The initial laboratory investigations revealed a WBC count (WBC) of  $226.0 \times 10^9/L$ , hemoglobin level of 109 g/L, and a platelet count of  $164 \times 10^9/L$ . Myeloid blasts were identified in 2% of the peripheral blood and 3% of the bone marrow aspirate. The karyotype was 46 XX t (9;22) (q34; q11) in all 20 metaphases analyzed. [20/20] Fluorescence in situ hybridization (FISH) analysis detected *BCR::ABL1* translocations in approximately 93% of nucleated cells. Notably, the quantitative real-time polymerase chain reaction (RT-PCR) yielded negative results for the *BCR::ABL1* transcript (P190, P210, and P230). Therefore, we conducted a new PCR detection test for some rare subtypes of expression, and finally find that of positive results for rare e1a3 *BCR::ABL1* transcript. An amplified band of 136 base pairs (bp) was observed using specific primers: the forward primer 5`CTGGCCCAACGATGGCGA` and reverse primer 5`GATGTAGTTGCTTGGGACCCA3`, which were parts of BCR e1 and ABL a3 regions, respectively. The fluorescent probe primer sequence used for quantitative analysis is: CCATTTTTGGTTTGGGCTTCACACCAT.

Eventually, the patient was diagnosed with chronic phase – CML (CP-CML) with e1a3 *BCR::ABL1* transcript, as confirmed by morphology, FISH and cytogenetic analyses (Figure 1A-C). She was promptly treated with regimens consisting of hydroxyurea and first-line TKI (tyrosine kinase inhibitor) Flumatinib at a daily dosage of 600mg. Notably, at the time of diagnosis in June 2021, the diagnostic workup was limited to bone marrow examinations, including morphology, flow cytometry, FISH and RT-PCR. Given the absence of symptom like headaches indicating central nervous system involvement, no imaging or lumbar puncture was initially performed. Consequently, the patient received standard treatment for CML with oral Flumatinib 600mg/day.

After three, six, nine, and twelve months of TKI treatment, the patient exhibited normal bone marrow morphology, flow cytometry-minimal residual disease (FCM-MRD), and FISH analysis, indicating the absence of accelerated phases or blast phase. Nevertheless, PCR assays persistently demonstrated a positive result of e1a3 expression. Regrettably, the level of e1a3 was only qualitatively analyzed and not quantitatively analyzed, and the patient has been maintained on oral treatment with flumatinib.

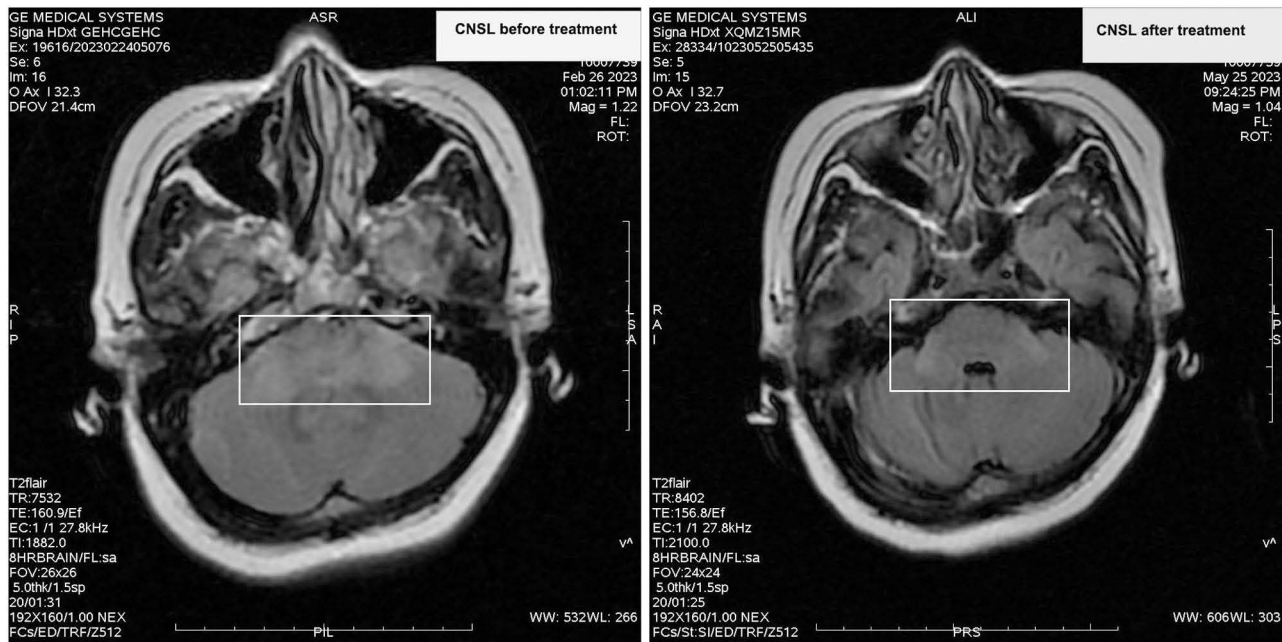
The patient exhibited symptoms of headaches, vomiting, and blurred vision up to 17 months after oral flumatinib (December 2022). Given the possibility of CNS invasion, the diagnostic tests were conducted. A brain magnetic resonance imaging (MRI) scan revealed abnormal signals in the medulla oblongata and bilateral pontine arms (Figure 2). The diagnostic lumbar puncture indicated that the patient has progressed to the chronic myeloid leukemia blast phase (BP-CML), revealing that the total number of nucleated cells in cerebrospinal fluid (CSF) was  $4091 \times 10^6/L$ , and closely resembled myeloid blasts morphologically. The immunophenotyping analysis of CSF revealed the presence of 86.8% myeloid blasts expressed CD34 and CD117. FISH analysis of CSF also demonstrated *BCR::ABL1* translocations in approximately 70% of nucleated cells (Figure 1G-I). Concurrently, a PCR quantitative analysis of e1a3 was performed and found that 3.18% of expression in the bone marrow (Table 1). Meanwhile, the bone marrow puncture was submitted, including the evaluation of bone marrow morphology, flow cytometry for minimal residual disease (MRD), and FISH tests. Notably, all these assessments from bone marrow returned negative results (Figure 1D-F). At present, the patient has been diagnosed with isolated CNS infiltrated and progressed to AML with e1a3 *BCR::ABL1* transcript.

Based on the above findings, we amended the treatment protocol. Initially, we transitioned the patient from flumatinib to third-generation TKIs olverembatinib (a novel small molecular oral third-generation *BCR::ABL1* inhibitor) at a daily dosage of 40mg.<sup>18</sup> Subsequently, the patient was promptly initiated on a triple intrathecal regimen comprising methotrexate (10mg), dexamethasone (5mg), and cytarabine (50mg). After 13 cycles of intrathecal chemotherapy, the FCM-MRD of CSF cytology continued to detect myeloid blasts, therefore, to the decision to administer intravenous chemotherapy to the patient initially, followed by allogeneic hematopoietic stem cell transplantation treatment (*Allo*-HSCT) was prompted. She received a supplementary IA chemotherapy regimen, comprising Idarubicin 10 mg on days 1–3 and Cytarabine 150mg every 12 hours on days 1–3. Radiotherapy was strongly recommended, but the patient



**Figure 1** Cellular morphology of bone marrow and CSF, FISH, karyotype, and immunophenotype. (A) Initial bone marrow smear (Wright-Giemsa  $\times 1000$ ) revealed markedly hypercellular marrow along with 3% blast; (B) FISH revealed signal for *BCR::ABL1* fusion with pattern of 1 yellow (fusion signal), 1 red, and 2 green; (C) Cytogenetic analysis of bone marrow showed a karyotype 46, XX, t (9;22) (q34; q11); (D-F) The bone marrow smear, FISH, and karyotype examination from bone marrow samples yielded normal results, when CNSL occurred. (G) When CNS infiltrated, CSF cytology showed blast characterized by rounded mononuclear immature cells with hyperchromatic nuclei (Wright-Giemsa  $\times 1000$ ). (H) Metaphase FISH image of blasts in CSF revealed signal for *BCR::ABL1* fusion with pattern of 1 yellow (fusion signal), 1 red, and 2 green; (I) The immunophenotyping results of CSF sample demonstrated the presence of abnormal cells expressing CD 45 and CD117. **Abbreviations:** CNSL: central nervous system leukemia; CSF: Cerebro-Spinal Fluid.

expressed a disagreement with the recommended course of treatment. After another 3 cycles of intrathecal chemotherapy, the CSF cytology turned to negative with no detectable myeloid blasts. Subsequently, the patient underwent an unrelated HLA-matched *Allo*-HSCT. On day 12 post-transplant, hematopoietic reconstruction was required, and the patient was discharged on day 45. To date, the patient has undergone eight lumbar punctures for detection post-transplantation, with negative FCM-MRD results in the cerebrospinal fluid and negative expression of *e1a3* in the bone marrow sample simultaneously, remaining disease-free and alive. Commencing 60 days post-transplant, the patient began taking



**Figure 2** MRI examination of the patient’s head. When CNSL occurred, T2 FLAIR images showed patchy high signal areas in the medulla and cerebellar peduncles. After treatment, the size of the lesion significantly reduced.

olverembatinib at an initial dose of 20mg every other day (qod), which was escalated to 30mg qod. By day 100 post-transplant, the dosage was increased to 40mg qod, a dose that has been maintained to date. The patient has expressed satisfaction with the treatment approach and the current outcomes.

**Table 1** EIA3 Expression and FCM-MRD Monitoring of This Patient

Time	Peripheral blood	Bone marrow	Cerebrospinal fluid	Symptoms and Treatments
2021.06	Positive			A high white blood cell count discovered
2021.10	Positive			Flumatinib 600mg/d from 06/07/2021
2022.01	Positive			Flumatinib 600mg/d
2022.08	Positive			Flumatinib 600mg/d
2023.01	Positive			Headache and vomiting
2023.02		Positive (3.18%)	FCM-MRD (+)	Change flumatinib to olverembatinib, and 9 cycles of intrathecal chemotherapy
2023.04		Positive (0.14%)	FCM-MRD (+)	Idarubicin and Cytarabine chemotherapy
2023.05		Negative (0%)	FCM-MRD (-)	Total of 16 cycles of intrathecal chemotherapy finished
2023.07		Negative (0%)		Allo-HSCT
2023.08		Negative (0%)		Lumbar puncture and intrathecal chemotherapy, olverembatinib
2023.09		Negative (0%)	FCM-MRD (-)	Olverembatinib oral
2023.11		Negative (0%)	FCM-MRD (-)	Olverembatinib oral
2024.07		Negative (0%)	FCM-MRD (-)	Olverembatinib, lumbar puncture and intrathecal chemotherapy



## Discussion

One of the key features of the e1a3 translocation is the absence of exon a2, and the deletion of *ABL1* exon a2 from the fusion transcript is predicted to lead to a protein lacking approximately two-thirds of the N terminus in the *Src* homology (SH3) domain.<sup>19</sup> The latter is crucial for full leukemogenesis *in vivo*. Because *BCR::ABL1* mutants deficient in the SH3 domain induce growth factor independence, leading to reduced proliferation of tumor cells *in vivo* due to diminished tissue invasiveness.<sup>20</sup> Therefore, the clinical course of CML patients with e1a3 *BCR::ABL1* fusion transcripts is characterized by a lower clinical progression, lower white blood cells (WBC) counts, and an extended duration in the chronic phase even in the absence of treatment.<sup>21</sup> However, the e1a3 and e1a2 (p190) transcripts have been reported to possess similar molecular weight and probably a similar clinical profile, thus it has been hypothesized that e1a3 fusion may predispose extramedullary infiltration and disease acceleration.<sup>22</sup> We present a case of CML with the e1a3 *BCR-ABL1* transcript, which is unique as it involves the emergence of an isolated CNS blast crisis, despite achieving hematological and cytogenetic responses.

Accurate diagnosis e1a3 CML is imperative. One concern is that it might be disregarded during routine testing procedures. The FISH assay employs probes that specifically target the breakpoints at both ends of the genes, thereby enabling the detection of various breakpoints within the *BCR* and *ABL1* genes. Moreover, the next-generation sequencing (NGS) can identify atypical translocations, rectifying the previously overlooked detection of this significant genetic events. If a *BCR::ABL1* negative result is obtained by conventional testing, then RT-PCR and NGS sequencing of RNA can facilitate the detection of this breakpoint to avoid misdiagnosis.<sup>23–25</sup> The case we reported was also diagnosed clearly through RT-PCR. Honestly, FCM plays an important role in the initial diagnosis of CML, in the blast phase, and in the differential diagnosis of MPN, mixed cell leukemia, and other conditions. However, PCR is more recommended for MRD monitoring, especially during the stable period.

Cases harboring the e1a3 *BCR-ABL1* transcripts have been reported in Acute Lymphoblastic Leukemia (ALL), AML, and CML. We conducted a literature review and found no reports of central nervous system invasion in several cases of the e1a3 subtype CML. This is the first reported case, and the treatment methods for these cases are not consistent (Table 2). The standard treatment for this condition has not been established. The e1a3 *BCR-ABL* gene encodes the ATP binding site of ABL kinase, which can be utilized for TKI-targeted therapy. ALL patients with e1a3

**Table 2** Cases of e1a3- CML in Literature

Case	Age	Sex	Diagnosis	WBC count at diagnosis × 10 <sup>9</sup> /L	Extramedullary lesions	Diagnostic method	Therapy	Transplant	Outcome	References
1	41	F	CML-CP	189.5	NA	RT-PCR and FISH	IFN- $\alpha$ + HU→IMA	NA	Complete cytogenetic remission	[19]
2	64	F	CML-CP	53.2	NA	RT-PCR and FISH	IFN- $\alpha$ + HU→IMA	NA	Complete cytogenetic remission	[19]
3	75	F	CML-CP	18.5	NA	RT-PCR and FISH	NA	NA	NA	[21]
4	68	F	CML-CP	38.4	NA	RT-PCR	IFN- $\alpha$ + HU	NA	Hematological remission	[24]
5	80	M	CML-BC	NA	NA	RT-PCR and DNA Sequencing	IMA	NA	Transformation to lymphoid blast crisis	[25]

(Continued)

Table 2 (Continued).

Case	Age	Sex	Diagnosis	WBC count at diagnosis $\times 10^9/L$	Extramedullary lesions	Diagnostic method	Therapy	Transplant	Outcome	References
6	49	M	CML-BC	8.5	Cervical mass	RT-PCR	Dasa	NA	Complete cytogenetic remission	[26]
Our case	56	F	CML-BC	226	CNS	RT-PCR and FISH	Fluma→Olv	Yes	Complete cytogenetic remission	

**Abbreviations:** CP, chronic phase, BC, blast crisis, IMA, imatinib, Dasa, dasatinib, Fluma, flumatinib, IFN- $\alpha$ , interferon- $\alpha$ , HU, hydroxyurea, Olv: olverembatinib, NA, not available, CNS, central nervous system, RT-PCR, reverse transcription-polymerase chain reaction.

BCR-ABL gene-positive who receive TKI-targeted therapy have a higher survival rate compared to those who do not receive TKI treatment, and the combination with allogeneic hematopoietic stem cell transplantation is more effective.<sup>22,23</sup> A case report has illustrated that the administration of dasatinib led to the regression of extramedullary blast crisis (cervical mass) in CML with e1a3 BCR-ABL1 fusion transcript.<sup>26</sup> If the T315i mutation was developed after treatment with dasatinib monotherapy, ponatinib therapy can be replaced.<sup>27</sup>

This is exactly the issue of TKI treatment resistance in CML, not limited to the e1a3 subtype. Imatinib has demonstrated efficacy in the e1a3 subtype of CML or ALL,<sup>27</sup> and our patient was initially treated with flumatinib. Flumatinib is a chemically derived form of imatinib with two modifications, enhances the specificity of its BCR::ABL1 inhibition.<sup>28</sup> It is recommended as the first line drug according to CML related consensus in China.<sup>29</sup> However, in this case, the treatment fails to produce satisfactory effects and progresses to an isolated CNS blast crisis in this case. The extramedullary proliferation of blast is an additional diagnostic indicator of BP-CML, regardless of the disease stage present in the bone marrow. The dissemination of leukemic cells in the CNS is linked to high WBC counts during the initial diagnosis.<sup>30,31</sup> One possible reason for the CNS infiltration observed in this case was the marked elevation in WBC count ( $226.0 \times 10^9/L$ ). Patients present with an isolated relapse in the CNS, underscoring the significant role of the CNS as a refuge for leukemic stem cells. In addition, flumatinib rarely pass through the blood-brain barrier, which is also the main reason. In cases with high white blood cell counts and persistent positivity in RT-PCR testing for e1a3, early MRI of the head and intrathecal chemotherapy should be performed to prevent central nervous system leukemia. This case provides a valuable lesson in the management of CML patients with e1a3 BCR::ABL1 transcripts.

The blood-brain barrier (BBB) permeability of Flumatinib was about 0–6%,<sup>32</sup> and the BBB permeability of olverembatinib was 2–12%, higher than the former.<sup>33</sup> Accordingly, when our patient presented with symptoms of CNS, we promptly transitioned from flumatinib to olverembatinib with the aim of increasing the drug concentration in the CSF. Simultaneously, systemic intravenous medication was administered to enhance the therapeutic effect. Finally, *allo*-HSCT was performed and olverembatinib was administered for continued maintenance treatment post-transplantation. On day 150 after transplantation, FCM-MRD of CSF was negative, and e1a3 expression of bone marrow was also negative (Table 1).

The advent of TKIs has transformed the treatment landscape for patients with BP-CML, providing new options and enabling remission for older and more fragile individuals, although it may be of shorter duration, through the use of single agents. However, there is a significant risk of relapse within a few months without *allo*-HSCT consolidation. The combination of *allo*-HSCT with TKI maintenance therapy has been shown to be an effective approach for treating BP-CML, especially for extramedullary disease.<sup>34–37</sup> Although studies on extramedullary BP-CML lack extensive data and mainly rely on case reports, it is crucial to treat patients with the same level of care as other BP-CML patients. Irrespective of the specific TKI selected, it is essential to incorporate systemic and /or intrathecal therapy within the overall approach to preventing and treating CNS leukemia. This is also the reason why our patient was successfully

treated. Till today, the e1a3 expression of our patient is still negative and quantity analysis of PB and BM are 0% after transplantation. Unfortunately, the e1a3 detection was inconsistency in this report, due to the absence of quantitative testing in the initial stage, the precise expression level remained unclear, and treatment measure was not promptly adjusted until the patient exhibited symptoms of the central nervous system. Most of the time, peripheral blood and bone marrow were tested, while cerebrospinal fluid testing was more important, which is the limitation of this case.

## Conclusion

Conventional diagnostic methods may overlook the e1a3-type CML, requiring a combination of RT-PCR, FISH, and other methods to ensure a definitive diagnosis about e1a3-type CML. Previous reports have shown that e1a3-type CML has a protracted disease course and is sensitive to TKIs. However, due to the high white blood cell count at diagnosis, the extramedullary invasion characteristic of the e1a3 subtype, and the limited ability of flumatinib to cross the blood-brain barrier, this case experienced a CNS blast crisis. Currently, no standardized treatment has been established. Moreover, *allo*-HSCT together with third-generation TKI maintenance therapy is suggested as an effective treatment approach.

## Abbreviations

CML, Chronic myeloid leukemia; BP, blastic phase; CP, chronic phase; WBC, white blood cell count; CNS, central nervous system; FISH, Fluorescence in situ hybridization; RT-PCR, real-time polymerase chain reaction; FCM-MRD, flow cytometry-minimal residual disease; CSF, cerebrospinal fluid; *Allo*-HSCT, allogeneic hematopoietic stem cell transplantation treatment.

## Ethics and Informed Consent

Consent for publication was obtained from the patient for her data included in the study. This retrospective study was approved by the Ethics Committee of the Second Affiliated Hospital of Army Medical University.

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## Disclosure

The authors have no conflicts of interest to disclose in this work.

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