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CASE REPORT

Isolated Central Nervous System Blast Crisis of Chronic Myeloid Leukemia with Dasatinib Therapy

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SUMMARY

Background: **Isolated central nervous system (CNS) blast crisis was uncommon in chronic myeloid leukemia (CML).**
Methods: **The present study reported an interesting case of a CML patient administered with dasatinib presenting with headache and seizure unconsciousness. Imaging investigation, immunophenotyping, bone marrow cytology inspection, chromosomal analysis, and polymerase chain reaction (PCR) were performed on a 41-year-old CML patient.**
Results: **Bone marrow examination revealed complete cytogenetic remission and there were no obvious abnormalities in head CT and MR. Cytomorphological examination of cerebrospinal fluid (CSF) showed 50% blasts. Flow cytometry analysis was showed 78.3% CSF cells expressing the specific myeloid antigens. PCR analysis on CSF cells was positive for BCR/ABL P210 fusion gene. All the above CSF findings were suggestive of CNS infiltrating isolated from bone marrow cytogenetic remission.**
Conclusions: **Isolated CNS blast crisis of CML with dasatinib were rare. The mechanism still remains unclear and the treatment regimen requires further exploration. Flow cytometry showed great value to detect the blast cells in this patient.**
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KEY WORDS

chronic myeloid leukemia, extramedullary blast crisis, central nervous system, dasatinib

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm of pluripotent stem cells and characterized by the oncogenic Philadelphia (Ph) chromosome and BCR-ABL P210 fusion gene. CML, presenting as leukemic infiltration of the central nervous system (CNS), may be associated with systemic progression or relapse, but isolated CNS blast crisis is uncommon. The application of tyrosine kinase inhibitors (TKIs) is capable of inducing complete cytogenetic and deep molecular remissions and has significantly improved the prognosis of patients with CML. In particular, studies have suggested that the second generation TKI dasatinib is more effective in penetrating the blood-brain barrier and

is used for the prevention and treatment of extramedullary CNS infiltrating [1]. We herein report a case administered with dasatinib who experienced the isolated CNS blast crisis. The mechanism still remains unclear and the treatment regimen requires further exploration.

CASE PRESENTATION

A 41-year-old man with recurrent headache for 20 days and seizure unconsciousness for 1 day was transferred to our emergency department. The patient had a history of CML for 4 years and was treated with imatinib (400 mg/d) for the first 2 years, but failed to achieve the optimal treatment response. In the last 2 years, he was administered with dasatinib (100 mg/d) and finally obtained the cytogenetic complete remission.

No neurological positive signs were revealed in physical examination. No abnormalities were found in CT of head, enhanced MR of brain, electrocardiogram, and echocardiography. Full blood count showed the following: leukocytes 5,410/mm^3; neutrophils 77.4%; lymphocytes 18.8%; monocytes 3.6%; eosinophils 0.1% and basophils 0.1%; hemoglobin 14.1 g/dL; platelet count 2.18 million/mm^3. CSF cells derived from lumbar puncture were examined and showed total white blood cells of 468/mm^3, which includes blasts 50%, basophils 44%, and neutrophils 6% (Figure 1A). The above CSF cells were also confirmed positive for the antigens of CD33, CD117, CD13 by flow cytometry (Figure 1B) and positive for the fusion gene of BCR/ABL P210 by polymerase chain reaction (PCR). In bone marrow and peripheral blood, flow cytometry showed that CD33, CD117, CD13, CD11C, and cMPO positive cells accounted for 1.2% (Figure 2A) and 0.5% (Figure 2B), respectively. Morphology showed that the percentage of blasts was less than 5% (Figure 2C). G-banding chromosome showed 46, XY (Figure 2D). PCR showed that the BCR-ABL P210 fusion gene transcript was 3.171% and mutations of tyrosine kinase ABL1 site were all negative. Finally, a confirming diagnosis of the isolated infiltration of leukemic cells in CNS outside bone marrow was made in the CML patient.

Intrathecal injection of cytarabine, methotrexate, and dexamethasone were administered through lumbar puncture after dehydration treatment. The symptoms of CNS disappeared quickly and the percentage of blasts from CSF also decreased, but the above symptoms and indicators both rebounded again after three intrathecal injections (Figure 3). Systemic chemotherapy of methotrexate (3 g/m^2·d twice) was added but invalid. Then, a medium dose of cytarabine (2 g/m^2·d twice) was used and blasts of CSF were gradually decreased. The blasts percentage and BCR-ABL P210 fusion gene transcript in CSF were both ultimately changed to negative within 5 weeks of diagnosis. Thereafter, the patient's treatment plans included dasatinib 140 mg once a day and intrathecal chemotherapy once a month, but allogeneic hematopoietic stem cell transplantation (allo-HSCT) was not considered due to financial reasons. To date, the case has maintained complete molecular remission, both intramedullary and extramedullary, for 12 months.

DISCUSSION

The percentage of extramedullary disease in the blast phase of CML is about 16% composed of 1% CNS infiltration [2]. TKIs have significantly improved the treatment response of CML patients [3]. If CNS leukemic infiltration occurs after obtaining complete cytogenetic and molecular proof, rare cases with isolated CNS blast crisis must be considered [4]. In the present study, the patient experienced isolated CNS blast crisis but has no evidence of bone marrow progress.

The pathogenesis of CNS leukemia is unclear, but systemic CML blast crisis is considered as the main cause. In particular, chromosomal abnormalities and gene mutations are related to CML blast crisis. Besides BCR/ABL fusion gene, p53, RUNX1, RAS, and others also undergo mutations during CML blast crisis [5]. Recent studies have revealed that although BCR/ABL kinase activity is sufficiently inhibited in patients treated with TKIs, drug resistance can be induced by BCR/ABL kinase independently or by ABL1 site mutant mechanisms. Different mutation types of ABL1 site have different sensitivities to different TKIs. Activation of the STAT3 signaling pathway is an important mechanism of BCR/ABL kinase independent TKIs' drug resistance [6]. Activation of the Wnt/β-catenin signaling pathway is also a characteristic of CML and contributes to stem cell proliferation [7]. RAF/MEK/ERK signaling pathway is enhanced after TKI treatment, which is related to the up-regulation of PRKCH, becoming a potential drug resistance mechanism [8]. In the present study, this case has no mutation of the ABL1 site and still has the sensitivity to dasatinib. So, this drug resistance might be not correlated with the ABL1 site mutant mechanism, but it is unclear whether it is related to the BCR/ABL kinase independent mechanism or not.

The leukemia cells can enter the CNS through the blood-brain barrier causing CNS leukemia. As imatinib has a relatively poor permeability to CNS, any leukemic cells in the CNS might not be able to receive the initial treatment of imatinib, leading to isolated CNS leukemia happen [9]. The second generation TKIs have improved penetration in the blood-brain barrier. Dasatinib has been proven effective on the basis of its superior CNS permeability [10], but there are still isolated cases of CNS blast crisis in patients treated with dasatinib [11]. Therefore, in addition to disease biology, dosage and drug levels of dasatinib might play a role in disease progression. It has been reported that the patient took less than 100 mg dasatinib once a day during the treatment process, which failed to prevent the progress of CNS leukemia. In the present study, although the patient achieved cytogenetic remission after 2 years of dasatinib, he did not achieve major molecular remission,

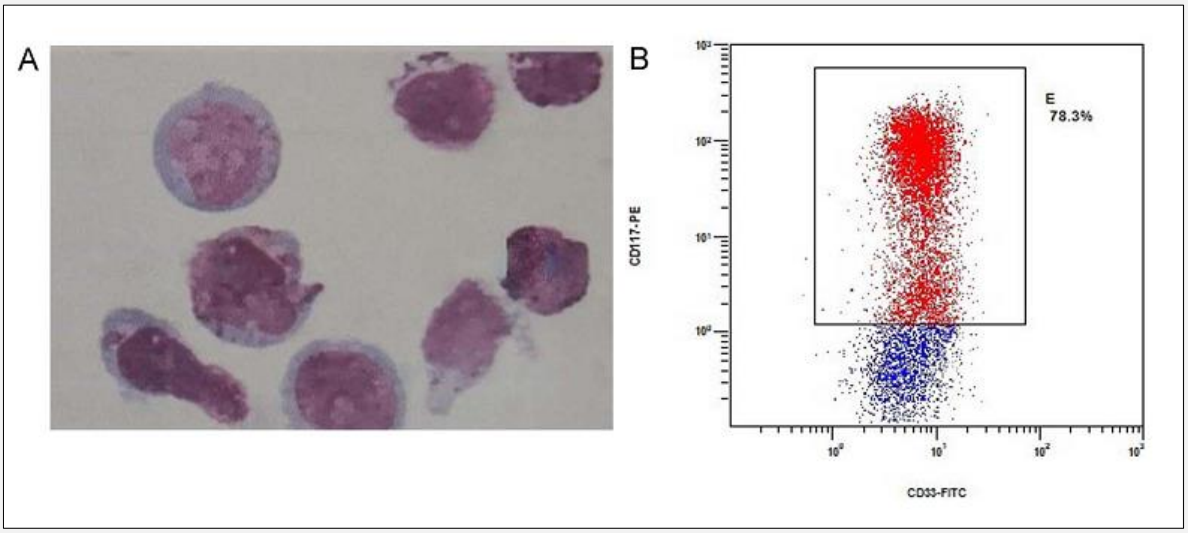

Figure 1. Analysis of CSF by cytology smear and flow cytometry: (A) Large accumulation of blast cells in CSF, (B) Flow cytometry was performed and showed that blast cells were positive for CD33 and CD117 in CSF.

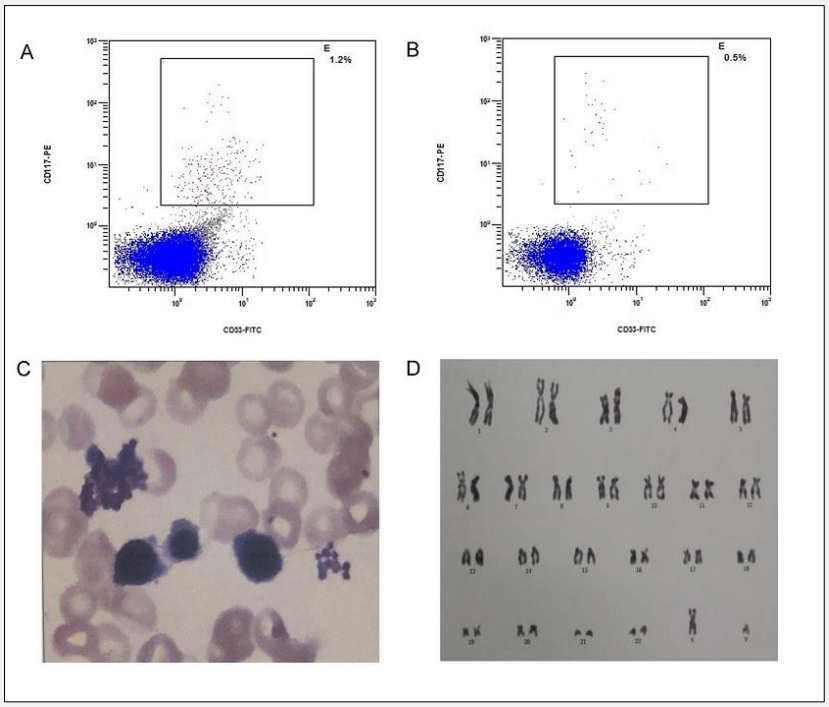

Figure 2. Analysis of bone marrow and peripheral blood by flow cytometry, cytology smear and chromosome: (A) Bone marrow immunotyping of CD33 and CD117 positive cells, (B) Peripheral blood flow cytometry showed CD33 and CD117 positive cells, (C) Bone marrow smears showed a normal bone marrow image (Giemsa stain, high power view), (D) G-banded karyotype of bone marrow analysis showed a Ph chromosome.

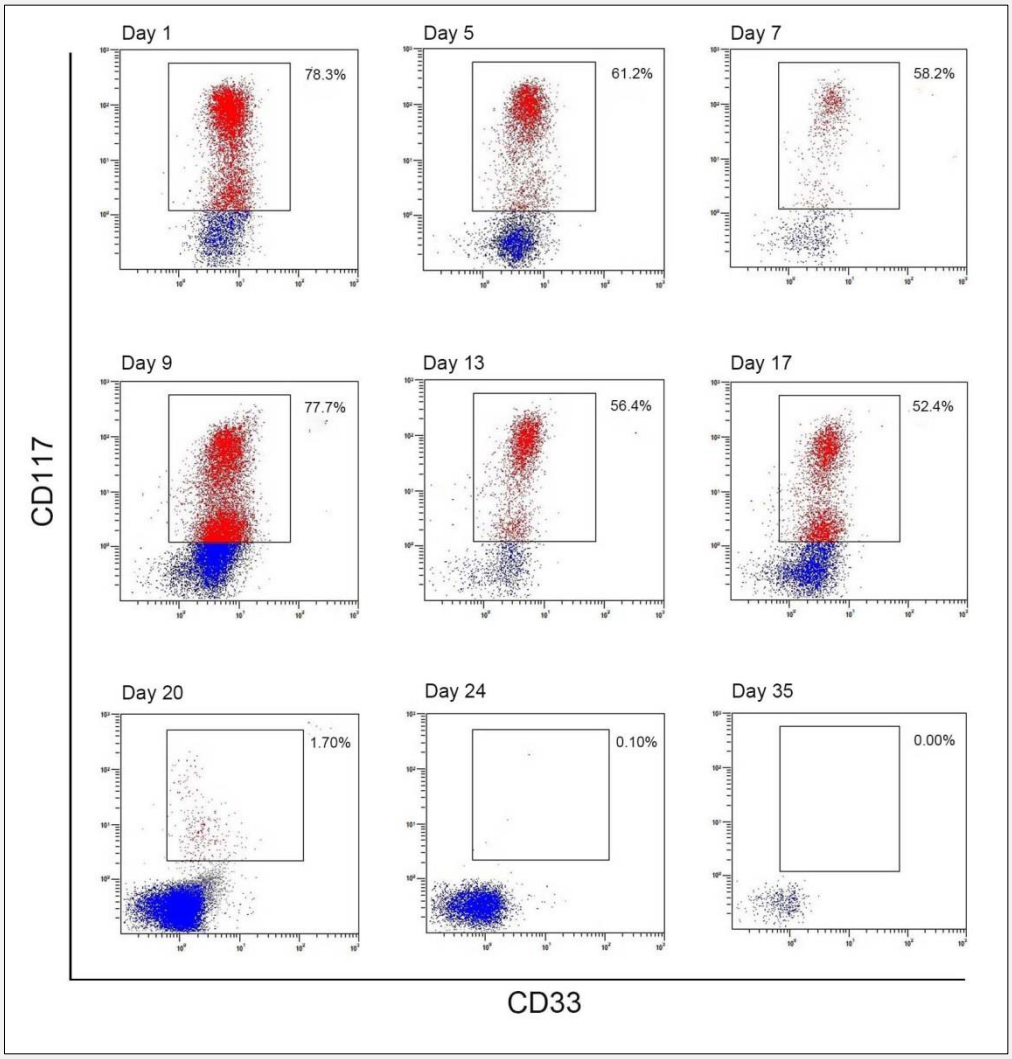

Figure 3. Analysis of CSF by flow cytometry during treatment: Blast cells after treating in CSF ($CD33^+CD117^+$cells/total nucleated cells).

Adding methotrexate chemotherapy on the day of 9 and 14 and cytarabine chemotherapy on the day of 18 and 32.

which might be related to inadequate dosage resulting in isolated blast crisis of CNS. So, the patient's treatment plans after again obtaining complete remission included dasatinib 140 mg once a day.

In summary, active strategies such as intrathecal chemotherapy combined with systemic chemotherapy, improved second-generation penetration of TKIs in CNS dose adjustment, and allo-HSCT, are regarded as potential effective therapies for CML patients with isolated CNS blast crisis [12]. Close monitoring and dose adjustment in time are also very important. Furthermore, it is necessary to further study the related molecular and immune mechanisms of isolated CNS blast crisis, providing the foundation to explore rational novel therapies [13].

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Statement of Ethics:
This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Institutional Review Board Institutional of the Affiliated Second Hospital of Anhui Medical University. The patients enrolled in the study each signed an informed consent to participate in and to publish this case.

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Declaration of Interest:
The authors have no relevant conflicts of interest.

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