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 extramedul-
ary CNS infiltrating [1]. We herein report a case ad-
ministered 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 opti-
tmal treatment response. In the last 2 years, he was ad-
ministered with dasatinib (100 mg/d) and finally obtained
the cytogenetic complete remission.

No neurological positive signs were revealed in physi-
cal examination. No abnormalities were found in CT of
head, enhanced MR of brain, electrocardiogram, and
echocardiography. Full blood counts showed the follow-
ing: leukocytes 5,410/mm³; neutrophils 77.4%; lympho-
cytes 18.8%; monocytes 3.6%; eosinophils 0.1% and
basophils 0.1%; hemoglobin 14.1 g/dL; platelet count
2.18 million/mm³. CSF cells derived from lumbar punct-
ture were examined and showed total white blood cells
of 468/mm³, 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 posi-
tive for the fusion gene of BCR/ABL P210 by polymer-
ase chain reaction (PCR). In bone marrow and peripher-
al 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 nega-
tive. Finally, a confirming diagnosis of the isolated in-
filtration 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 punc-
ture 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 metho-
trexate (3 g/m²·d twice) was added but invalid. Then, a
medium dose of cytarabine (2 g/m²·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 intra-
theal chemotherapy (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 in-
filtration [2]. TKIs have significantly improved the
response of CML patients [3]. If CNS leukemic
infiltration occurs after obtaining complete cytogen-
etic 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 sys-
temic CML blast crisis is considered as the main cause.
In particular, chromosomal abnormalities and gene mu-
tations 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 ki-
rase independently or by ABL1 site mutant mecha-
nisms. Different mutation types of ABL1 site have dif-
f erent 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 path-
way 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 sensi-
tivity 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

Therefore, in addition to disease biology, dosage and
drug levels of dasatinib might play a role in disease pro-
gression. 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 dasati-
nib, 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].

Acknowledgment:
The authors thank the patient and all the investigators including the physicians, nurses, and laboratory technicians in this study.
**Isolated CNS Blast Crisis of CML**

**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.

**Source of Funds:**
This work was supported by grants from National Natural Science Foundation of China (Number: 81670179) and University Natural Science Research Project of Anhui Province (Number: KJ2019A0254).

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

**References:**