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Case Report

The overwhelmingly positive response to Dasatinib of a patient with multiple blast crisis of chronic myeloid leukemia

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Abstract: Blastic phase (BP), the terminal phase of chronic myeloid leukemia (CML), can occur in any of the hematopoietic lineages. Extramedullary blastic crisis (EBC) is a rare form of blastic crisis, which has an extremely poor prognosis. As the tyrosine kinase inhibitor (TKI), Dasatinib is a more effective treatment drug than Imatinib and Nilotinib for this type of CML, because it has greater potency and penetrates through the blood-brain barrier to reach the cerebrospinal fluid (CSF). This report examines the case of a 22-year-old woman with CML, who successively suffered from monocytic blast crisis, lymphoid blast crisis, and central nervous system EBC. She had an overwhelmingly positive response to taking Dasatinib and eventually achieved lasting complete remission.

Keywords: Dasatinib, chronic myeloid leukemia, blastic crisis.

Background

Chronic myeloid leukemia (CML) is a malignant clonal disease affecting the hematopoietic stem cells, which is caused by the Philadelphia (Ph) chromosome, a chromosomal aberration. This translocation juxtaposes the ABL gene (chromosome 9) and the BCR gene (chromosome 22) to create a BCR-ABL fusion gene [1]. CML has a median onset age of 53 years and occurs in one to two people per every 100,000 [2]. The clinical course of CML can be divided into three phases, which include the chronic phase (CP), the accelerated phase (AP), and the blastic phase (BP). Patients in the BP respond poorly to a variety of treatments and have a weak prognosis [3]. Extramedullary blastic crisis (EBC) is a rare type of blastic crisis. Although EBC has a low occurrence rate, its prognosis is extremely poor.

Imatinib, the first BCR-ABL tyrosine kinase inhibitor (TKI) introduced in CML clinical practice, has proven to be remarkably effective in the treatment of CML patients. Nilotinib, the second BCR-ABL TKI developed, is a more potent and selective inhibitor of the BCR-ABL protein tyrosine kinase and has demonstrated success in thwarting the majority of known BCR-ABL mutations that resist Imatinib [4]. Dasatinib has more potency than both Imatinib and Nilotinib and can swim through the blood-brain barrier to reach the cerebrospinal fluid (CSF) [5].In several preclinical and clinical reports, Dasatinib demonstrated a significantly better penetration of the central nervous system (CNS) than Imatinib [6-10, 15].

This paper reports the case of a 22-year-old female with CML, who suffered successive monocytic and lymphoid blast crisis. Extramedullary blast crisis affecting the CNS also appeared. At last, the patient responded well to Dasatinib and achieved lasting complete remission (CR).

Case presentation

In February 2011, a 22-year-old female was hospitalized after two months of fever, cough, sputum, chest tightness, palpitation, and shortness of breath. She had a body temperature of 37.8 degrees Centigrade. Her spleen was palpable at roughly 2 cm below the left costal mar-

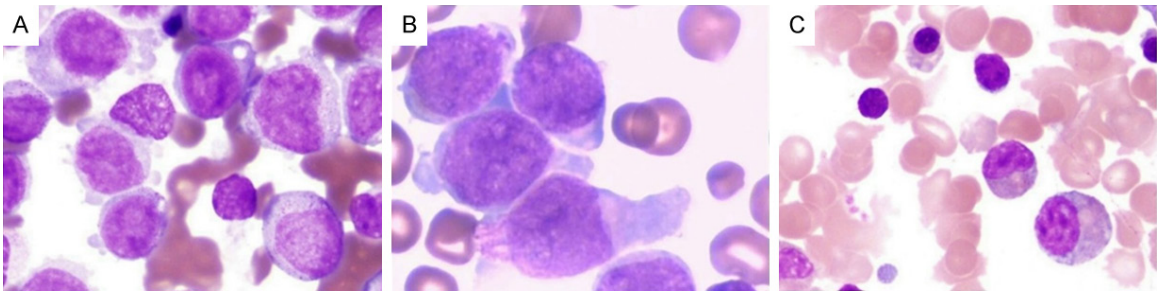

Figure 1. Bone marrow cytology results. A: Acute mononuclear transformation of CMLin February 2011. Bone marrow smear revealed mononuclear abnormal hyperplasia (1000×). B: Acute lymphocytic transformation of CML in November 2011. Bone marrow smear showed lymphocytic abnormal hyperplasia (1000×). C: Bone marrow complete remission in May 2014 (1000×).

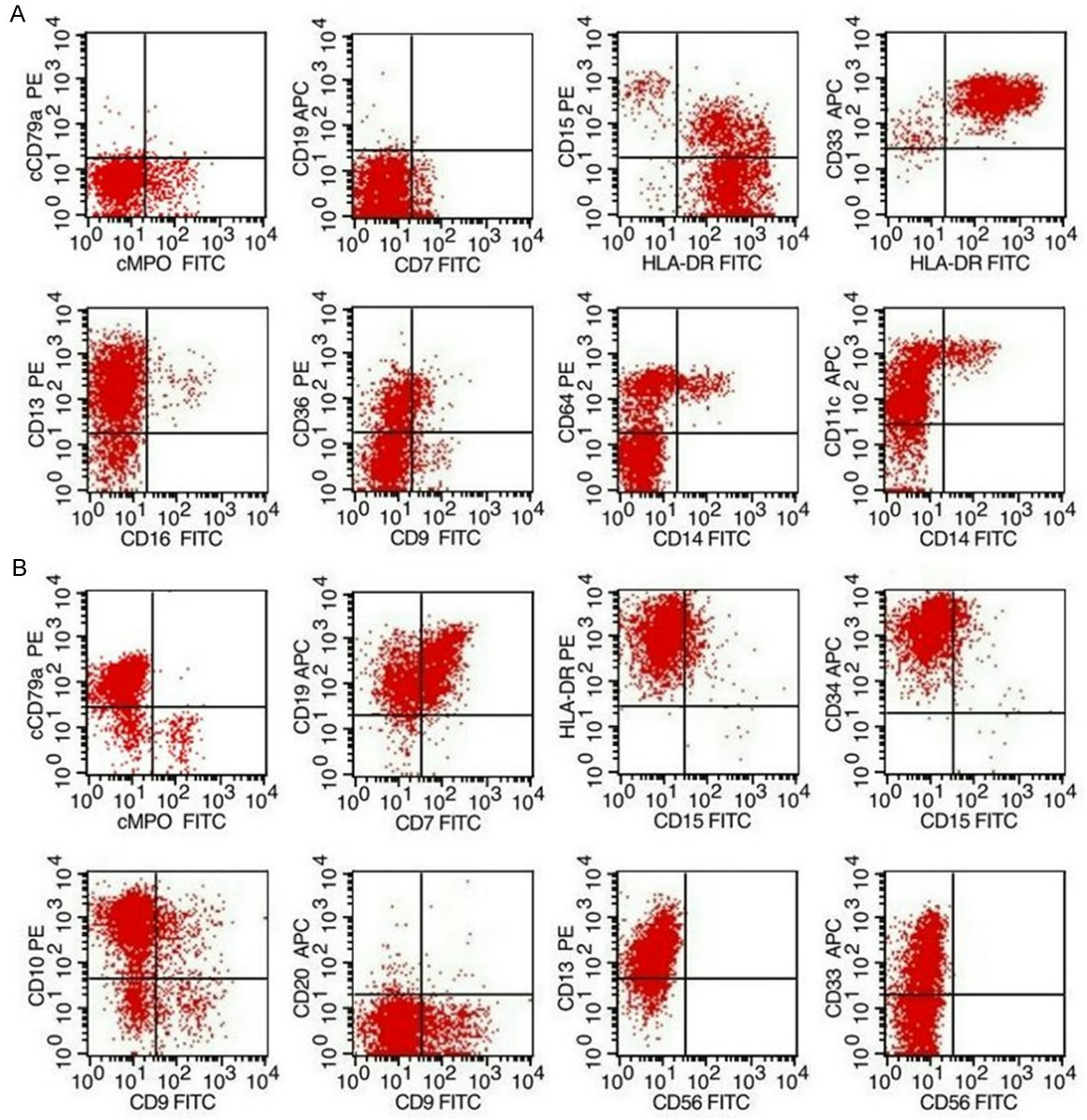

Figure 2. Bone marrow flow cytometry results. A: Monocytic crisis of CML: 72.94% nucleated cells were malignant myeloid blasts, possibly primitive and immature mononuclear blasts, which expressed HLA-DR, CD33, CD13, CD11c;

partly expressed CD64, CD15, CD36; less expressed CD34, cMPO; and didn't express CD7, CD19, cCD79a, cCD3, CD14, CD16, CD9, CD2, CD56. B: Lymphoid crisis of CML: 74.53% of nucleated cells were malignant B-lineage immature cells with myeloid expression. Those cells expressed CD19, CD10, CD34, HLA-DR, CD13, cCD79a; partly expressed CD7, CD9; less expressed CD15; and didn't express CD64, CD20, CD56, CD2, IgM, cMPO, and cCD3.

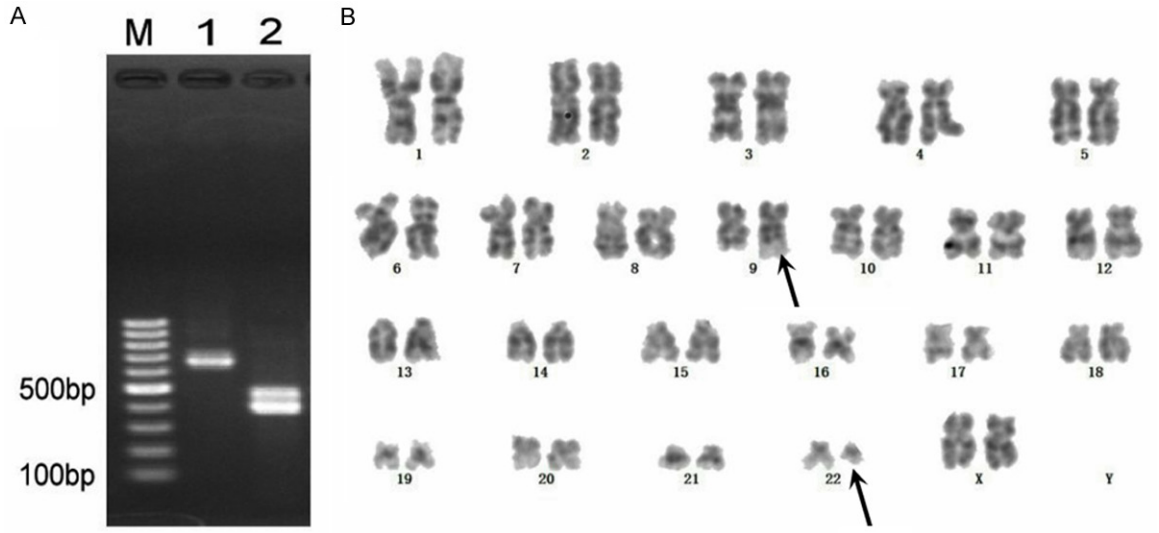

Figure 3. BCR/ABL gene and Chromosome examination results. A: Positive BCR/ABL gene (P210) (M: marker, 1: the patient, 2: internal control). B: Chromosome 9 and chromosome 22 reciprocal translocation.

gin. The patient had a non-remarkable family history. Blood tests showed a hemoglobin (Hb) concentration of 38 g/L, a red blood cell count (RBC) of 1.18×10^{12}/L, and a platelet count (PLT) of 105×10^{9}/L. She had a white blood cell count of 187.04×10^{9}/L with 88% juvenile cells, 2% band forms, 5% segmented cells, 1% acidophils, 1% basophils, and 3% lymphocytes. A bone marrow smear showed 88.8% primitive and immature mononuclear cells (**Figure 1A**). A bone marrow flow cytometry (FCM) analysis revealed that 72.94% of the nucleated cells were malignant myeloid blasts. These possibly primitive and immature mononuclear blasts expressed HLA-DR, CD33, CD13, CD11c; partially expressed CD64, CD15, CD36; barely expressed CD34, cMPO; and didn't express CD7, CD19, cCD79a, cCD3, CD14, CD16, CD9, CD2, and CD56 (**Figure 2A**). The Ph chromosome and the BCR-ABL fusion gene (P210) were observed during cytogenetic analysis (**Figure 3**). The BCR-ABL (P210) fusion gene had a quantitative result of 110.61%. The BCR-ABL fusion gene kinase domain mutation analysis did not show any drug-resistant mutations. Finally, monocytic crisis of CML was definitely diagnosed. The patient achieved complete remission after a combination of chemotherapy (Pirarubicin 40 mg/m^2 d1-d3, Cytarabine 100 mg/m^2 d1-d7) with Gleevec (400 mg, bid, p.o.). After that, she received consolidation chemotherapy with high-dose Cytarabine, while continually taking Gleevec. As a result, the patient demonstrated continuous hematologic and molecular complete remission.

In November 2011, there was a clear increase in the patient's white blood cells. Blood tests showed WBC 40.50×10^{9}/L, with 68% juvenile cells, RBC 3.05×10^{12}/L, Hb 103 g/L, and PLT 90×10^{9}/L. A bone marrow smear revealed lymphatic hyperplasia, with 92.5% primitive and immature lymphocytes (**Figure 1B**). A bone marrow FCM analysis showed that around 74.53% of the nucleated cells were malignant B-lineage immature cells with myeloid expression. Those cells expressed CD19, CD10, CD34, HLA-DR, CD13, cCD79a; partially expressed CD7, CD9; barelyexpressed CD15; and did not express CD64, CD20, CD56, CD2, IgM, cMPO, or cCD3 (**Figure 2B**). The quantitative results of the BCR-ABL (P210) fusion gene were 170.51%. Therefore, lymphoid blast crisis of CML was diagnosed. The patient was prescribed a VDCLP regimen chemotherapy (Vincristine 2 mg d1, 8, 15, 22; Daunorubicin

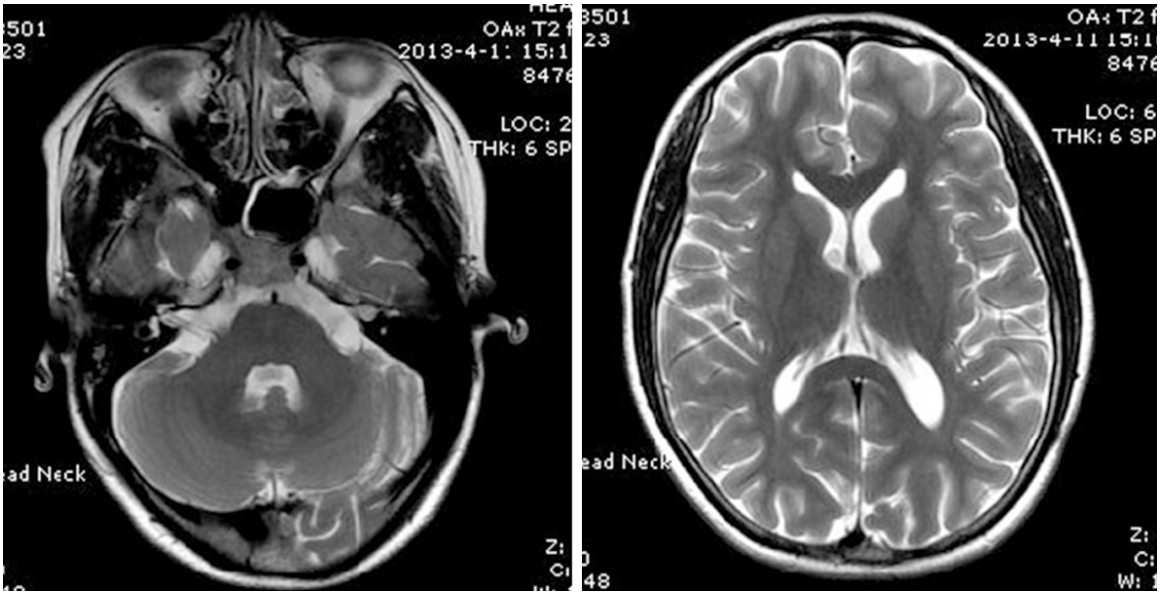

Figure 4. Cranial magnetic resonance imaging results. Meningeal enhancement was in bilateral temporal dura mater and tentorial, in accordance with meningeal leukemia.

40 mg/m^2 d1-d3; Cyclophosphamide 750 mg/m^2 d1, 15; L-Asp 6000 IU/m^2 d11, 14, 17, 20, 23, 26; and Prednisone 1 mg/kg·d d1-14, reduced to stop d15-28), with Nilotinib (400 mg, bid, p.o.) and drug intrathecal injection. After this treatment, the patient once again achieved complete remission and was prescribed Nilotinib for maintenance treatment.

In May 2012, the patient felt scalp tingling, throbbing pain, numbness in her lower limbs, diminished eyesight in her left eye, and hearing loss in her right her. However, a bone marrow smear did not show any obvious abnormality. The quantitative result of the BCR-ABL (P210) fusion gene was 2.76%. A great number of juvenile cells were detected in the cerebrospinal fluid. CNS extramedullary blastic crisis was finally diagnosed. As treatment, the patientwas given intermittent drug intrathecal injection (a combination of Cytarabine 100 mg, Methotrexate 0.5 g, Dexamethasone 5 mg every time) and Dasatinib (100 mg/d, p.o.). By June 2012, the patient's condition had quickly improved. From then on, the patient insisted on oral Dasatinib and drug intrathecal injection as treatment and as a result, achieved hematologic and molecular complete remission. No immature cells were discovered in the cerebrospinal fluid.

In April 2013, the patient again felt numbness in her lower limbs. Immature cells were found again in the CSF and cranial magnetic resonance imaging (MRI) suggested that the meningeal enhancement was in bilateral temporal dura mater and tentorial, which aligned with meningeal leukemia (**Figure 4**). After this diagnosis, the patient received radiation therapy in addition to the Dasatinib. She was given local radiotherapy to her entire brain and spinal cord eighteen times. In detail, the brain was given 36 Gy/20F from April 22 to May 20, and the spinal cord was given 30.6 Gy/17F from April 22 to May 15. Through June 2013, she did not have any discomfort. Bone marrow smear implied complete remission, and the BCR-ABL fusion (P210) gene was negative. No immature cells were detected in the CSF.

Since June 2013, the patient has been only taking Dasatinib (100 mg, qd), without other chemotherapy or radiation therapy. As of May 2014, the patient's hematology and molecular biology were still in continuous complete remission. Specifically, bone marrow smear (**Figure 1C**) showed complete remission, and the BCR-ABL fusion (P210) gene was negative. Additionally, the meningeal leukemia did not relapse again.

Discussion

Blast crisis of the CML has a variety of original cell proliferation types: myeloid-type blast crisis (MBC) accounts for about 60%-80%; lymphoid-

type blast crisis (LBC) accounts for 20-30%; and the total proportion of erythroid-type, megakaryocytic-type, mixed-type and biphenotypic-type blast crisis is less than 5% [11]. CML developing different types of blast crisis is extremely rare.

The patient in this case was first diagnosed with monocytic crisis of the CML in February 2011, and was diagnosed with lymphoid crisis the second time in November 2011. Due to the different blast crisis types, the patient was given corresponding chemotherapy regimens involving Imatinib or Nilotinib, and additional supportive treatment. Eventually, both the monocytic and the lymphoid blast crisis of the CML reached complete remission. Currently, the mechanism of successive differing types of blast crisis is not clear. The different blast crises may be a result of abnormal proliferation of various cloned hematopoietic stem cells, or may be related to gene rearrangement or mutations appearing during the process of chemotherapy.

Extramedullary blast crisis (EBC) is a rare type of chronic myelogenous leukemia blast crisis [12]. As reported, extramedullary blast crisis can occur in any part of body, including the lymph nodes, bones, skin, the central nervous system (CNS), the pleura, soft tissue, and urogenital system. The incidence of EBC is low, and no standard treatment currently exists. No matter what type of chemotherapy is prescribed, the prognosis will be extremely poor. In this case, the patient suffered extramedullary blast crisis affecting the CNS for the third time in May 2012. The patient once again achieved complete remission after a treatment of Dasatinib, drug intrathecal injection, and radiotherapy. For nearly a year following these results, the patient had a lasting hematologic and molecular complete remission through only taking Dasatinib. While the traditional treatment of CNS leukemia includes drug intrathecal injection and radiotherapy, the shorter survival times and easy relapse indicates these therapies are less effective than Dasatinib [13]. The patient's good prognosis was not only due to intrathecal injection and local radiotherapy, but also to the important role of Dasatinib in her treatment.

Dasatinib, a second-generation inhibitor of tyrosine kinases, has demonstrated significant progressin adults with Imatinib/Nilotinib-resistant or intolerant CML. The drug has a significantly different structure than Gleevec [16, 17]. Dasatinib has much greater potency (325-fold) than Imatinib and has been shown to be active at low or subnanomolar concentrations, which may allow a therapeutically effective concentration of Dasatinib to work effectively. The increased potency and the low-protein environment of the cerebrospinal fluid (CSF) where Dasatinib is likely to exist as a free drug suggest that even relatively low levels of Dasatinib in the CNS will be sufficient for anti-tumor activity [15]. In addition, Dasatinib penetrates through the blood-brain barrier more easily than Imatinib [6, 8-10, 14, 15]. In fact, many studies [13-17] have reported that Imatinib was not effective in controlling central nervous system leukemia, because it's inability to penetrate through the blood-brain barrier did not prevent central nervous system (CNS) relapses. Porkka K *et al* [15] proved that Dasatinib had anti-tumor effects in a mouse model of intracranial CML, and that these benefits could be transferred to the clinic so that Dasatinib could induce substantial responses in patients with CNS Ph+ leukemia.

Other mechanisms in addition to BCR-ABL may be responsible for extramedullary disease expansion, including the activation of Src family kinases [18, 19]. Dasatinib not only has potent inhibitory effects on BCR-ABL, but also inhibits the Src family [14]. In contrast, neither Imatinib nor Nilotinib act against targets like the Src-family of tyrosine kinases, which is why this study chose Dasatinib instead of Nilotinib to give the patient when she had CNS EBC.

To the best of our knowledge, this is the first report of a patient with CML developing different types of hematologic blast crisis and CNS EBC, then taking Dasatinib, responding positively, and achieving lasting complete remission. Our case suggests that Dasatinib has superior efficacy over Imatinib/Nilotinibin CNS EBC patients with CML. Lasting hematologic and molecular remission could be achieved in patients with Imatinib/Nilotinib-resistant CML.

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Disclosure of conflict of interest

None.

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