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Case report

Myodesopsia is a symptom of central nervous system blast crisis in chronic myeloid leukemia

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ABSTRACT

A 49-year-old woman diagnosed with chronic myeloid leukemia in the chronic phase was started on dasatinib treatment, after which she complained of myodesopsia. Nineteen months after diagnosis, the patient again complained of myodesopsia and developed bilateral optic neuritis. Cerebrospinal fluid analysis revealed an increase in blasts, although peripheral blood and bone marrow examination confirmed that the patient remained in a molecular response to tyrosine kinase inhibitor (TKI) therapy. The patient was diagnosed with an isolated central nervous system blast crisis, a rare occurrence with second-generation TKI therapy, and the initial presentation of myodesopsia represented a symptom of this condition.

1. Introduction

Tyrosine kinase inhibitors (TKIs) have dramatically improved the prognosis of patients with chronic myeloid leukemia (CML), and have decreased the prevalence of blast crisis (BC) in this population. Isolated central nervous system blast crisis (CNS BC) is rare in CML, and its mechanism remains unknown. Symptoms of CNS BC can vary. At diagnosis, our patient presented with myodesopsia, which may have represented an initial symptom of the infiltration of CML cells into the CNS. Although peripheral blood and bone marrow revealed a molecular response, an increase in blasts only in the CNS can potentially occur. Given its rarity, however, the actual clinical features of this condition are not adequately described. Symptoms of disease progression might therefore be less typical, requiring additional vigilance on the part of the physician.

1.1. Case

A 49-year-old woman was admitted to hospital with an elevated white blood cell (WBC) count and platelet count but without any other symptoms. The initial peripheral blood laboratory evaluation revealed a WBC count of 27,500 cells/μL (neutrophils 77.6%, lymphocytes 13.6%, monocytes 2.2%, eosinophils 1.9%, basophils 4.7%), hemoglobin of 12.7 g/dL, and platelet count of 174.9×10^4 cells/μL. No coagulopathy was observed. Bone marrow examination showed a total nucleated cell count of 43.5×10^4 cells/μL. Karyotype analysis revealed 46, XX, t(9;22)(q34;q11.2) in 20/20 cells, and fluorescence *in situ* hybridization of BCR/ABL was 98% positive. Sokal risk stratification was high.

The patient was diagnosed with CML in the chronic phase, and treatment with 100 mg dasatinib once daily was initiated.

Three months after the diagnosis, the patient achieved a complete cytogenetic response (CCyR), but complained of various indefinite symptoms in the interim. One week after starting dasatinib therapy, the patient complained of myodesopsia, although a physical examination and non-contrast computed tomography revealed no abnormalities. The myodesopsia persisted for 1 month and subsequently resolved. The patient then started to complain of headache, which was atypical and difficult to describe (the patient used expressions such as: 'I feel that metal is squished in my head', or, 'I feel a strange feeling like graveling'). Contrast magnetic resonance imaging (MRI) was performed, but revealed no abnormality. After these symptoms resolved, the patient began to complain of throat constriction and difficulty in swallowing. At the same time, she experienced edema in the face and extremities. We considered these symptoms to be adverse events of dasatinib, and discontinued the patient from dasatinib therapy at 1 year after the diagnosis of CML. At this point, the patient was in MR4 (real-time quantitative polymerase chain reaction [RT-PCR]; international scale, BCR-ABL IS), considered an optimal response under the European Leukemia Net criteria, and was switched to nilotinib 400 mg/day. The patient was still in MR4 at 18 months after diagnosis. From 12 months to 18 months after diagnosis, the patient again complained of various

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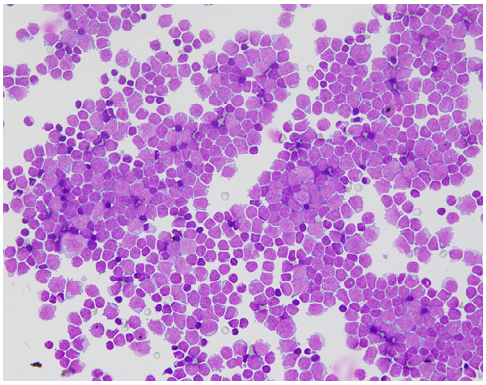

Fig. 1. (a) Axial T1-weighted images demonstrated left optic nerve thickening. (b) Cerebrospinal fluid cytology showed elevated myeloid immature blasts. Wright-Giemsa stain, original magnification × 100.

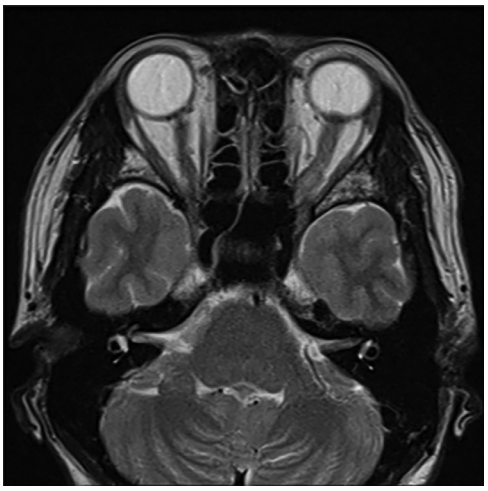

Fig. 1. (*continued*)

indefinite symptoms, such as heartburn, cough, and unexplained headache. All examinations to determine the cause of these symptoms were negative. Nineteen months after diagnosis, the patient experienced molecular failure, with an increase in IS from 0.0073% to 0.0163%. The patient was switched to 100 mg/day bostinib, and simultaneously complained of myodesopsia of the left eye. The symptom worsened and vision in both eyes gradually diminished until the patient was diagnosed with bilateral optic neuritis using contrast MRI (Fig. 1a). Steroid therapy and plasma exchange were initiated, but without a successful outcome.

Because the patient's bilateral optic neuritis was refractory to the treatment, we examined the cerebrospinal fluid (CSF) and found an increased WBC count (1636 cells/mm^3), indicative of myeloid immature blasts (Fig. 1b). BCR-ABL mRNA levels in CSF were determined by RT-PCR and found to be 3.0×10^6 copy/μg RNA. The patient was therefore diagnosed as having CNS BC of CML. However, peripheral blood testing revealed no elevation of IS, bone marrow examination remained normal, and the patient remained in MR4. Thus, the patient was diagnosed with isolated CNS BC and was treated with intrathecal methotrexate, cytarabine, dexamethasone, and whole brain irradiation. Despite the MR4 stage of the patient, bostinib therapy was switched to 30 mg/day ponatinib, which is currently ongoing.

2. Discussion

Treatment with TKIs has dramatically improved the prognosis of patients with CML, reducing progression to advanced-phase CML or BC to 1%–1.5% per year compared with more than 20% per year in the pre-imatinib era [1,2]. Isolated CNS BC is particularly rare, although some cases have been reported even following TKI therapy. Although the ability of imatinib to penetrate the CNS is poor [3], dasatinib has been shown to better penetrate the blood-brain barrier (BBB) than imatinib in a mouse model of acute lymphoid leukemia (ALL) [4].

Various symptoms of CNS BC have been described, including headache and vomiting, which are typical symptoms of brain tumor. However, an initial symptom of visual disturbance is rare, and we have identified only one previous report of a patient with CNS BC experiencing bilateral visual loss [5]. Our patient complained of myodesopsia at diagnosis, and in retrospect, CML cells might have been present in the CNS at this early stage, although we did not examine the CFS at diagnosis and MRI of the head revealed no abnormality. In a previous report of a patient with CML BC having CML cells in the CSF at diagnosis [6], dura thickening was identified by MRI of the head, leading to the discovery of CNS invasion. However, the patient in this case was in the blast phase, in which infiltration of CML cells into the CNS can be expected, whereas our case was in the chronic phase. Cell infiltration into the CNS might accompany an increase in cell number, although the mechanism of isolated CNS BC remains unknown.

As a potential reason for this discrepancy, the permeability of the BBB by dasatinib might have been insufficient to suppress the CML cells. In the ALL mouse model study described above, dasatinib was shown to have greater BBB permeability than imatinib [4]. However, this finding represents a single report of the BBB permeability of dasatinib, and was performed in a pre-clinical study. The permeability of TKIs across the BBB in humans may differ from that in mice, and no studies examing the BBB permeability of third generation TKIs have been reported to date.

Another explanation is that the tumor microenvironment of the CNS might differ from that of bone marrow. The brain is rich in oxygen and glucose, facilitating tumor growth. Thus, CML cells may increase in the CNS in isolation, while the bone marrow remains in molecular response.

We identified 24 cases of isolated CNS BC [5,7], of which 18 cases received imatinib, five cases had undergone stem cell transplantation, and one case was refractory on ponatinib therapy. To date, few studies of isolated CNS BC with second-generation TKI therapy have been reported. CNS BC is particularly rare, and no effective treatment strategy has been established, although previous reports have examined treatment with an intrathecal cytotoxic agent, radiation, systemic chemotherapy, or stem cell transplantation.

In conclusion, we report a rare case of CNS BC in a patient with CML receiving second-generation TKI therapy in which myodesopsia might have represented an initial symptom of CNS involvement. The patient might have had CML cells in the CNS already at diagnosis. Our report indicates that it is necessary to identify the mechanism of isolated onset of CNS BC so that appropriate treatment for this condition can be developed.

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Conflict of interest

The authors declare no competing financial interest in relation to the work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2019.03.001.

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