Revista Colombiana de Cancerología

Octubre - Diciembre / 2022 Rev Colomb Cancerol. 2022;26(4):448-452

CASE REPORT

Isolated central nervous system blast crisis in chronic myeloid leukemia under treatment with dasatinib. A case report and literature review

Crisis blástica aislada del sistema nervioso central en la leucemia mieloide crónica en tratamiento con dasatinib. Reporte de un caso y revisión de la literatura

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Fecha de sometimiento: 27/11/2021, fecha de aceptación: 18/01/2022
Disponible en internet: 30/12/2022
https://doi.org/10.35509/01239015.836

Abstract

Chronic myeloid leukemia (CML) is a disease that occurs in three phases: chronic, accelerated, and blast crisis. Blast crisis is diagnosed when there are 20% or more blasts in the bone marrow or extramedullary blast infiltration, frequently in the form of myeloid sarcoma. Isolated central nervous system blast crisis is very rare and even more in patients treated with dasatinib, which has good penetrance at this level. We present the case of a 61-year-old patient with a long-term diagnosis of CML under treatment with dasatinib, maintaining a major molecular response, who consulted for headaches and seizures, ruling out anatomical and infectious causes. CSF analysis showed the presence of blasts with a normal bone marrow biopsy, which led to the diagnosis of isolated central nervous system blast crisis. Dasatinib treatment continued at a higher dose, and an intrathecal chemotherapy regimen with Ommaya reservoir was established, with excellent results. Isolated central nervous system blast crisis is rare; most cases have been reported under treatment with imatinib, which has low penetrance at this level. There is only one case in the literature of blast crisis treated with dasatinib, and it has lymphoid origin. Management is not well established due to limited literature on the subject. Multicenter studies are required to delineate an adequate treatment in this case type.

Keywords: blast crisis, chronic myeloid leukemia, central nervous system

Resumen

La leucemia mieloide crónica (LMC) es una enfermedad que se presenta en tres fases: crisis crónica, acelerada y blástica. El diagnóstico de crisis blástica se establece cuando hay 20% o más de blastos en la médula ósea o infiltración extramedular de blastos, frecuentemente en forma de sarcoma mieloide. La crisis blástica aislada del SNC es muy rara y más aun en pacientes tratados con dasatinib que tiene buena penetrancia a este nivel. Presentamos el caso de un paciente de 61 años con diagnóstico a largo plazo de LMC, en tratamiento con dasatinib, manteniendo una respuesta molecular mayor, que consultó por cefalea y convulsiones, descartando causas anatómicas e infecciosas. El análisis de LCR mostró la presencia de blastos con una biopsia de médula ósea normal que llevó al diagnóstico de crisis blástica aislada del sistema nervioso central. Se continuó el tratamiento con dasatinib a una dosis más alta y se estableció un régimen de quimioterapia intratecal con reservorio de Ommaya con excelentes resultados. La crisis blástica aislada del sistema nervioso central es rara, en la mayoría de los casos se ha notificado bajo tratamiento con imatinib, que tiene baja penetrancia a este nivel. Solo hay un caso en la literatura de crisis blástica tratada con dasatinib y es de origen linfoide. El manejo no está bien establecido debido a la literatura limitada sobre el tema. Se requieren estudios multicéntricos para delinear un tratamiento adecuado en este tipo de casos.

Palabras clave: crisis blástica, leucemia mielógena crónica, sistema nervioso central

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Introduction

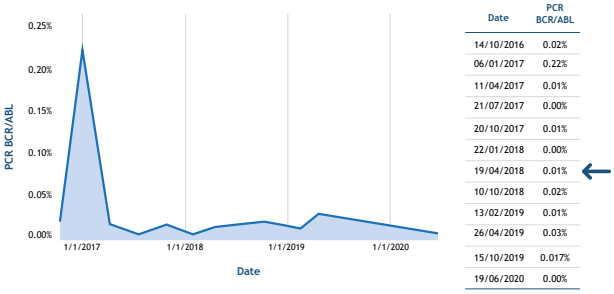
Chronic myeloid leukemia (CML) is a disease characterized by the translocation between chromosomes 9 and 22, which is called the Philadelphia chromosome, and can be diagnosed at the onset in a chronic phase, an accelerated phase, or a blast crisis (1, 2). The necessary criteria for the diagnosis of blast crisis are either an infiltration greater than or equal to 20% in the bone marrow or extramedullary blast proliferation, such as a myeloid sarcoma. The cellular origin can be myeloid, lymphoid, and others that are less frequent (2, 3, 4). Progression to blast crisis is exotic in patients who achieve and maintain a major molecular response, with central nervous system (CNS) involvement being very rare in this context. Nevertheless, when it occurs, it does so in the context of systemic relapse, often of lymphoid cellular origin (5). The majority of cases have been reported in patients treated with imatinib (6, 7, 8, 9, 10, 11, 12). There is only one case reported in the literature of a patient treated with dasatinib as an exclusive relapse of the central nervous system, after having presented a first blast crisis of lymphoid origin (13).

Herein we present the first case reported in the literature of an isolated central nervous system blast crisis of myeloid cellular origin in a patient treated with dasatinib.

The patient's relatives signed the informed consent to provide their data, and the institutional Ethics Committee authorized the publication of the clinical case.

Case description

A 61-year-old woman with a history of hypothyroidism managed with levothyroxine (50 micrograms a day) and Philadelphia-positive chronic myeloid leukemia since 2001. She received initial treatment with hydroxyurea and interferon, then initiated imatinib treatment at a dose of 400 mg from 2004 to 2008 when she developed loss of hematological response and subsequent myeloid blast crisis that required treatment with conventional 7 + 3 chemotherapy (7 days of cytarabine and 3 days of idarubicin), returning to the chronic phase of the disease without having documented secondary CNS involvement at that time. She started treatment with dasatinib 100 mg per day since 2009 with an adequate hematological response, achieving a greater molecular response and maintaining it to date (Figure 1).



Date	PCR BCR/ABL
14/10/2016	0.02%
06/01/2017	0.22%
11/04/2017	0.01%
21/07/2017	0.00%
20/10/2017	0.01%
22/01/2018	0.00%
19/04/2018	0.01%
10/10/2018	0.02%
13/02/2019	0.01%
26/04/2019	0.03%
15/10/2019	0.017%
19/06/2020	0.00%

Figure 1. Behavior of the BCR/ABL1 transcription showing the achievement and maintenance of a major molecular response to date. Blue arrow indicates the date of diagnosis of isolated central nervous system blast crisis.

She consulted the emergency department on April 24, 2018, complaining of holocranial headache of 20 days duration, emesis, and dysarthria. During evaluation at the emergency unit, she presented a convulsive state managed with benzodiazepines and phenytoin. Orotracheal intubation and transfer to the intensive care unit were necessary due to seizures.

Simple CT scan of the central nervous system was normal without meningeal enhancement, and complete blood count and blood chemistry on admission showed no alterations. A CNS MRI described extensive leptomeningeal infiltration of supratentorial and infratentorial locations due to a history of suspected relapse of chronic myeloid leukemia versus meningitis (Figure 2).

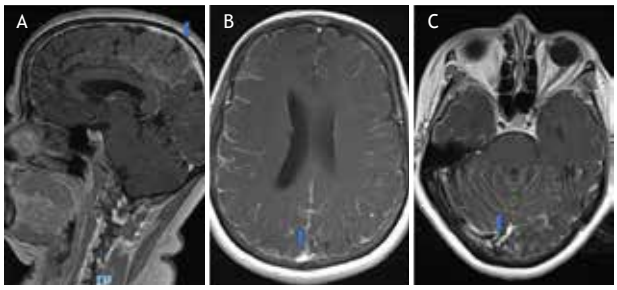


Figure 2. Cerebral MRI with DWI and ADC sequences showing extensive diffuse leptomeningeal enhancement with involvement of both cerebral hemispheres and the cerebellum (Blue arrows). Panel A: Sagittal; Panel B and C: Axial.

A cerebrospinal fluid study was carried out in which no microbiological isolation was found. Nevertheless, the Wright stain showed a hypercellular sample, infiltrated by numerous large immature cells (Figure 3), confirming the myeloid origin by flow cytometry (Figure 4).

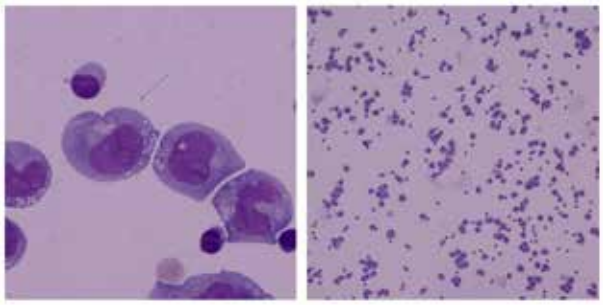


Figure 3. CSF cytological study showed the presence of immature cells with blast appearance. Arrow in the left frame shows a monoblastic cell in CSF. Wright stain 100X in the left frame and 10X in the right frame.

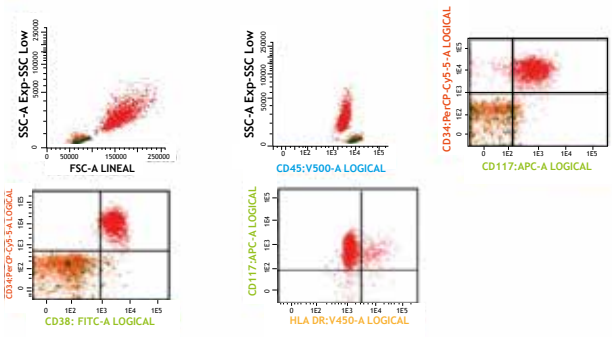


Figure 4. CSF flow cytometry showed the presence of 80.5 immature myeloid cells/microliter suggestive of myeloblasts (red events) with expression of CD117, CD34, CD38, partial expression of HLA DR, and weak CD45.

Therefore, it was established that the patient had isolated central nervous system blast crisis of myeloid origin.

It was decided to continue with dasatinib therapy but increasing the dose to 140 mg per day, associated with intrathecal chemotherapy with methotrexate 15 mg and cytarabine 40 mg twice weekly through Ommaya reservoir, until CNS remission was achieved during hospitalization (Figure 5).

The patient was discharged on June 25, 2018, continuing with weekly intrathecal chemotherapies for one month and then monthly until completing one year of treatment through Ommaya reservoir. She developed moderate to severe white matter alteration and hydrocephalus for which she required ventriculoperitoneal bypass.

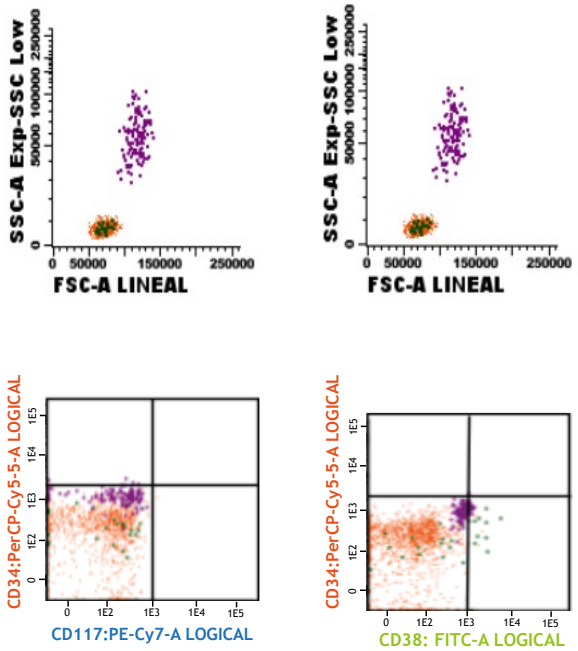


Figure 5. CSF flow cytometry, where no immature myeloid population is detected after treatment with intrathecal chemotherapy, denoting complete remission of the disease.

Currently the patient is alive and completed 32 months of remission (major molecular response and negative CSF during the last controls), with moderate functional dependence.

Discussion

CML is a triphasic disease that can be detected in a chronic phase, an accelerated phase, or blast crisis (1). The criteria for blast crisis consist of an infiltration greater than or equal to 20% in the bone marrow or extramedullary blast proliferation, such as a myeloid sarcoma, where the vast majority (at least 70%) are of myeloid cellular origin and up to 30% are usually of lymphoid origin (2). We have previously reported another rarer origin, which is myelomastocytic (3).

The mechanisms responsible for the transition from chronic phase to blast crisis in CML are not clearly delineated, although it might be reasonable to think that an increased BCR/ABL1 activity in hematopoietic stem cells is responsible for this transformation. It is not clear how this can occur exclusively in the CNS (4).

Progression to blast crisis is exotic in patients who achieve and maintain a major molecular response. When it occurs, it is suggested by the presence of signs and symptoms characteristic of acute leukemia (nocturnal diaphoresis, weight loss, fever, bone pain, symptoms related to anemia and bleeding) (5).

CNS involvement is rare in blast crisis, but when it occurs, it does so in the context of a systemic relapse, often of lymphoid cellular origin (5).

Cases have been reported in children and most adults treated with imatinib, which is possible due to the limited penetration of this drug into CSF given the presence of P-glycoprotein in the blood-brain barrier and the non-use of prophylactic intrathecal chemotherapy in patients who have had a first blast crisis (6-12). There is only one case reported in the literature of a patient treated with dasatinib as an exclusive relapse of the central nervous system, after having presented a first blast crisis of lymphoid origin, which may be plausible due to the cellular origin (13).

Our clinical case is the first in the literature of an isolated central nervous system blast crisis of myeloid cellular origin, possibly as a relapse of a first myeloid blast crisis 10 years earlier.

The presentation of this clinical picture is reported in the scarce literature with larval neurological symptoms, such as headache, cranial nerve involvement, and other less frequent signs such as seizures (6-11). Our patient presented with an aggressive behavior, leading the patient to having a seizure status that required sedative treatment and ventilatory support in the intensive care unit. Treatment is not well established and may include the use of systemic chemotherapy, holocranial radiotherapy, and exclusive intrathecal chemotherapy (12,13). In our case, it was decided to increase the dose of dasatinib given the achievement and maintenance of molecular remission, and the use of intrathecal methotrexate and cytarabine twice a week until blast clearance, once a week for a month, and then every month for up to one year using an Ommaya reservoir. Two years after finishing treatment, the patient is having a moderate functional dependence but an adequate quality of life and is in remission of the disease. The development of hydrocephalus needing ventriculoperitoneal bypass was probably associated with blast infiltration (14).

In conclusion, isolated central nervous system blast crisis is extremely rare in a patient who has molecular remission. Its form of presentation can vary from symptoms as general as headache to seizures, which can reach convulsive state. Simple imaging may not show changes; thus, it may be necessary to perform a contrast nuclear magnetic resonance imaging to identify masses or meningeal enhancement. A complete cerebrospinal fluid study that includes a cytological study and flow cytometry is necessary, and it is also important to rule out systemic relapse.

Treatment is not well established due to the lack of literature; however, it may involve systemic chemotherapy, holocranial radiotherapy, or exclusive intrathecal chemotherapy, depending on the type of compromise, which can be parenchymal, leptomeningeal, or cranial nerve paralysis.

The fact that an isolated central nervous system blast crisis has occurred as a relapse of a first systemic blast crisis opens the door for a discussion of the need to evaluate the use of prophylactic intrathecal chemotherapy regardless of the lymphoid or myeloid cell origins.

Special thanks to the hematopathology and radiology services of the Instituto Nacional de Cancerología (15, 5).

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