A Chronic Myeloid Leukemia Patient Presented With an Unusual Relapse in Central Nervous System: A Case Report

Mais Musleh[1] and Qossay ALHUSEIN[2]

[1]Al Assad University Hospital
[2]Al-Mouwasat University Hospital

November 15, 2023

A Chronic Myeloid Leukemia Patient Presented With an Unusual Relapse in Central Nervous System: A Case Report

Mais Musleh, MD[1], Qossay Al Husein, MD[2]

Authors:

[1]Mais Musleh, MD Department of hematology, Faculty of Medicine, Damascus, Syria.

[2]Qossay Al Husein, MD Department of hematology, Faculty of Medicine, Damascus, Syria.

Emails :

Mais Musleh: mais125@yahoo.com

Qossay Al Husein: qossay20@yahoo.com

CORRESPONDING AUTHOR :

Mais Musleh, MD hematology, AL-Assad University Hospital, Faculty of Medicine, Damascus, Syria.

Syria, Rif-Dimashq, Sahnaya, Al-Azroni Street.

Mobile phone: +963958203968

E-mail: mais125@yahoo.com

ORCID: https://orcid.org/0000-0002-2148-2921

Declarations :

Acknowledgment : Not applicable.

Competing interests : The authors declare that they have no conflicts of interest.

Funding : No funding was required.

Ethical approval and consent to participate : Not required for this case report.

Availability of data and materials : Not applicable. All data (of the patient) generated during this study are included in this published article and its supplementary information files.

Consent for publication : Written informed consent was obtained from the patient for publishing this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Guarantor : Qossay Al Husein is the guarantor of this work.

Author's contributions :

Mais Musleh: design of the study, data collection, data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript.

Qossay Al Husein: data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript.

Abstract :

Extramedullary involvement of the central nervous system (CNS) in Chronic Myeloid Leukemia (CML) is an uncommon occurrence for relapse. In this case report, we present the unique instance of a 43-year-old male diagnosed with CML who experienced a blast crisis involving CNS.

Key Word:

Central Nervous System, Chronic Myeloid Leukemia, Blast Crisis, Tyrosine Kinase Inhibiter

Abbreviations :

CNS: Central nervous system

CML: Chronic myeloid leukemia

CP: Chronic phase

TKI: Tyrosine kinase inhibitor

CSF: Cerebrospinal fluid

Introduction :

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder involving increased proliferation of the granulocytes without loss of differentiation capacity. It is defined by the presence of the Philadelphia chromosome, which results from a reciprocal translocation between chromosomes 9 and 22, specifically t(9;22)(q34:q11). this translocation leads to the fusion of the break point cluster region (BCR) with the ABL gene, which forms an oncogene, the transcript of which is an oncoprotein with a tyrosine kinase function [1]. CML is most frequently diagnosed in the chronic phase (CP) although it can less commonly present as an accelerated crisis or even progress to an acute leukemia, known as a blast crisis. Approximately 80% of blast crises manifest as acute myeloid leukemia, with the remaining cases being acute lymphoblastic leukemia. Treatment with the first-generation tyrosine kinase inhibitor (TKI), imatinib, achieves complete hematologic, cytogenetic, and molecular remissions in approximately 90%, 70%, and 30% of patients, respectively [2,3]. In rare instances, extramedullary involvement may occur, such as the presence of soft tissue leukemic infiltrates in various sites, which can be termed chloroma, myeloblastoma, or myeloid sarcoma [2–4, 7–10]. CML patients rarely present with a CNS blast crisis, which is typically reported in patients undergoing imatinib treatment [7–14]. The occurrence of CNS blast crisis is likely attributed to the limited penetration of the drug through the blood-brain barrier, making the CNS a sanctuary site [15,16]. This report describe an extramedullary rare case of 43-year-old male with CML who experienced an extramedullary blast crisis in the central nervous system. Treatment options and monitoring of disease response are discussed.

Case report :

We present the case of a 43-year-old male who was diagnosed with CML six years ago and had been undergoing treatment with imatinib 400 mg once daily. He presented with symptoms of headache and left eye ptosis, as figure (1), without exhibiting any other neurological or systemic manifestations. On physical examination, he appeared as a generally healthy young male with a normal-sized spleen and stable vital signs.

Upon initial assessment, his laboratory tests indicated normal levels of electrolytes, liver and kidney function, but high lactate dehydrogenase level of 896 U/l. His complete blood counts revealed a hemoglobin level of 9.1 g/dl, a white blood cell count of 40,000 × 10ˆ9/l, and a platelet count of 120 × 10ˆ9/l, with a peripheral blood smear showed left shifted neutropilic with 4% myeloid blasts.

Subsequent bone marrow aspiration and biopsy confirmed an accelerated-phase CML diagnosis. BCR-ABL oncogene analysis by polymerase chain reaction yielded a positive result of 0.36%. Brain CT scans revealed multiple lesions around the cerebral ventricular area, as figure (2).

Due to the absence of a prior history and due to his CNS symptoms and signs, treatment switched to dasatinib 100 mg once daily. Unfortunately, after a period of two months, the neurological symptoms worsened. Subsequently, the patient underwent intrathecal of the cerebrospinal fluid, which was found to contain cloudy yellowish cerebrospinal fluid (CSF) with atypical/blast CML cells, confirming the presence of CNS extramedullary myeloid blast infiltration, as figure (3). Furthermore, flow cytometry analysis of the bone marrow aspiration supported a diagnosis of blast-phase CML with immunophenotyping positive for CD 13, CD 33, CD 34, CD 117, MPO, HLA-DR. Analysis of the BCR-ABL oncogene through PCR revealed a elevated in positive result of 1.22%.

Treatment for the patient was adjusted to continue dasatinib at a daily oral dose of 100 mg. Additionally, an induction therapy (7 + 3) was initiated, consisting of Cytarabine 100 mg/m2 and doxorubicin 45 mg/m2, along with 7 doses of intrathecal methotrexate/ Cytarabine/ dexamethasone. Unfortunately, the patient experienced prolonged pancytopenia and multiple infections, which were compounded by the patient's overall poor general condition. The patient has continued to receive dasatinib 100 mg orally daily, being followed by 3 monthly PCR for BCR-ABL oncogene from peripheral blood and annual fluorescence in situ hybridization test from BM aspirate. He remains in complete cytogenetic and molecular remission with no current evidence of active extramedullary disease 3 months prior to writing this report.

Discussion:

Although CML has become an indolent illness in the majority of patients, blast crises remain severe and often life-threatening complications, necessitating aggressive disease management and, when possible, preparation for allogeneic stem cell transplantation (allo-SCT). CNS involvement is not typical for CML, although it has been well described. Seeding of the CNS by leukemia cells is seen more often with high WBC counts at presentation [3]. Nevertheless, our patient continues in good condition without any signs of extramedullary disease relapse.

In cases of CNS blast crisis, patients often manifest clinical and radiological symptoms akin to those seen in meningitis or encephalitis. The cerebrospinal fluid (CSF) typically tests positive for myeloid or lymphoid blasts. In some instances, molecular testing of the CSF has even identified the characteristic BCR-ABL oncogene [8]. Our patient initially presented with left eye ptosis. While we didn't confirm the presence of the BCR-ABL oncogene in the CSF, there was a substantial presence of myeloid blasts in the CSF, and the BCR-ABL oncogene was clearly detectable in the patient's peripheral blood and bone marrow.

Our case patient presented with a remarkable clinical feature, specifically, left eye ptosis, without concurrent neurological symptoms, alongside a left-shifted moderate neutrophilic condition. Furthermore, the absence of an enlarged spleen made it less likely to consider a long-standing case of CML. This distinct clinical presentation presented a considerable diagnostic challenge. In such clinical scenarios, a comprehensive analysis of CSF to detect atypical cells or blasts is of paramount importance. This is because initiating appropriate therapy promptly can play a pivotal role in preventing lasting neurological deficits.

Traditional therapies for treating CNS involvement by Philadelphia-positive leukemia, such as radiotherapy, intrathecal chemotherapy, and high-dose systemic chemotherapy, have yielded unsatisfactory results with short-lived responses [17]. Managing such cases necessitates a well-considered choice of a tyrosine kinase inhibitor (TKI) with enhanced blood-brain barrier penetration, in addition to systemic and CNS-directed therapy. Dasatinib, a second-generation TKI, demonstrates a 325-fold greater potency in inhibiting the

BCR-ABL oncogene in vitro compared to imatinib [18]. In our case, we opted for dasatinib over the first-generation TKI imatinib, as it has shown the ability to effectively penetrate the blood-brain barrier and provide sustained responses in CNS Philadelphia-positive leukemias [19]. There is an urgent need for novel strategies to treat such complicated cases, perhaps by incorporating therapies used for primary CNS cancer, such as high-dose methotrexate or temozolomide. Dasatinib may have an important role in managing CNS CML blast crises, especially when combined with whole brain radiation therapy.

Conclusion:

Maintaining a high level of vigilance is essential when it comes to detecting CNS involvement in CML patients who have received imatinib treatment, especially those in a blast crisis. Aggressive treatment strategies, including intrathecal chemotherapy, adjusting TKI for better CNS penetration, and even considering allogeneic stem cell transplantation, are crucial in such cases. Additional research is warranted to improve the concept of CNS prophylaxis for high-risk patients.

References :

1. Rowley JD: Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290–293. https://doi.org/10.1038/243290a0
2. Kantarjan HM, Keating MJ, Talpaz M: Chronic myelogenous leukemia in blast crisis: analysis of 242 patients. Am J Med 1987;83:445–454. DOI: 10.1016/0002-9343(87)90754-6
3. Canellos G: Clinical characteristics of the blast phase of chronic granulocytic leukemia. Hematol Oncol Clin North Am 1990;4:359–376. DOI: 10.1016/S0889-8588(18)30492-1
4. Specchia G, Palumbo G, Pastore D, Mininni D, Mestice A, Liso V: Extramedullary blast crises in chronic myeloid leukemia. Leuk Res 1996;20:905–908. DOI: 10.1007/s12288-014-0471-4
5. Matsuda M, Morita Y: Extramedullary blast crisis derived from 2 different clones in the central nervous system and neck during complete cytogenetic remission of chronic myelogenous leukemia treated with imatinib mesylate. Int J Hematol 2005;81:307–309. DOI: 10.1532/IJH97.04188
6. Ganessan K, Goel R, Kumar K, Bakhshi S: Biphenotypic extramedullary blast crisis as a presenting manifestation of Philadelphia chromosome-positive CML in a child. Pediatr Hematol Oncol 2007;24:195–198. DOI: 10.1080/08880010701198787
7. Al-Rayes HM, Al-Shaikh AA, Halim MA, Al-Qurashi FS, Al-Jurf MM: Leukemic synovitis as a presentation of myelomonocytic blast crisis of chronic myeloid leukemia. Saudi Med J 2001;22:808–811. https://pubmed.ncbi.nlm.nih.gov/11590459/
8. Jin GN, Zou P, Chen WX, Ding ZY, Zhou H: Fluorescent in situ hybridization diagnosis of extramedullary nodal blast crisis. Diagn Cytopathol 2013;41:253–256. DOI:10.1002/dc.21795
9. Shune L, Cayci Z, Rogosheske J, Brunstein C, Ustun C: Extramedullary blastic crisis in abdominal lymph nodes in a patient with chronic myelogenous leukemia on imatinib. Leuk Res 2012;36:e131–e132. DOI: 10.1016/j.leukres.2012.02.024
10. Yu HH, Lu MY, Lin DT, Lin KH, Tang JL, Jou ST: Pathological fracture as a manifestation of extramedullary blastic crisis in chronic myelogenous leukemia: report of one case. Acta Paediatr Taiwan 2006;47:150–154. https://pubmed.ncbi.nlm.nih.gov/17078470/
11. Rajappa S, Uppin SG, Raghunadharao D, Rao IS, Surath A: Isolated central nervous system blast crisis in chronic myeloid leukemia. Hematol Oncol 2004;22:179–181. DOI: 10.1002/hon.737
12. Radhika N, Minakshi M, Rajesh M, Manas BR, Kumar MD: Central nervous system blast crisis in chronic myeloid leukemia on imatinib mesylate therapy: report of two cases. Indian J Hematol Blood Transfus 2011;27:51–54. DOI: 10.1007/s12288-011-0055-5
13. Kim Hj, Jung CW, Kim K: Isolated blast crisis in CNS in a patient with chronic myelogenous leukemia maintaining major cytogenetic response after imatinib. J Clin Oncol 2006;24:4028–4029. DOI: 10.1200/JCO.2006.05.5608
14. Bornhauser M, Jenke A, Freiberg-Richter J, Radke J, Schuler US, Mohr B, et al: CNS blast crisis of chronic myelogenous leukemia in a patient with major cytogenetic response in bone marrow associated

with low levels of imatinib mesylate and its N-desmethylated metabolite in cerebral spinal fluid. Ann Hematol 2004;83:401–402. DOI: 10.1007/s00277-003-0829-4

15. Wolff NC, Richardson JA, Egorin M, Ilaria RL Jr: The CNS is a sanctuary for leukemic cells in mice receiving imatinib mesylate for Bcr/Abl-induced leukemia. Blood 2003;101:5010–5013. DOI: 10.1182/blood-2002-10-3059
16. Isobe Y, Sugimoto K, Masuda A, Hamano Y, Oshimi K: Central nervous system is a sanctuary site for chronic myelogenous leukemia treated with imatinib mesylate. Intern Med 2009;39:408–418. DOI: 10.1111/j.1445-5994.2009.01947.x
17. Cortes J: Central nervous system involvement in adult acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2001;15:145–162. DOI: 10.1016/s0889-8588(05)70203-3
18. O'Hare T, Walters DK, Stoffregen EP, Jia T, Manley PW, Mestan J, et al: In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res 2005;65:4500–4505. DOI: 10.1158/0008-5472.CAN-05-0259
19. Porkka K, Koskenvesa P, Lundan T, Rimpilainen J, Mustjoki S, Smykla R, et al: Dasatinib crosses the blood-brain barrier and is an efficient the therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood 2008;112:1005–1012. DOI: 10.1182/blood-2008-02-140665

Hosted file

`Figure 1.docx` available at https://authorea.com/users/513063/articles/687057-a-chronic-myeloid-leukemia-patient-presented-with-an-unusual-relapse-in-central-nervous-system-a-case-report

Hosted file

`Figure 2.docx` available at https://authorea.com/users/513063/articles/687057-a-chronic-myeloid-leukemia-patient-presented-with-an-unusual-relapse-in-central-nervous-system-a-case-report

Hosted file

`Figure 3.docx` available at https://authorea.com/users/513063/articles/687057-a-chronic-myeloid-leukemia-patient-presented-with-an-unusual-relapse-in-central-nervous-system-a-case-report