Panacea Journal of Medical Sciences 2024;14(3):886–888

Content available at: https://www.ipinnovative.com/open-access-journals

Panacea Journal of Medical Sciences

Journal homepage: http://www.pjms.in/

Case Report

Chronic myeloid leukemia in lymphoid blast crisis with extramedullary CNS infiltration in a pediatric patient: A case report

Mintu Ann Joy[1], **Vandana Bhatti**[1], **Ravneet Singh Heer**[1]*, **Kripa M Mathews**[1]

[1]*Dept. of Pathology, Christian Medical College and Hospital, Ludhiana, Punjab, India*

ARTICLE INFO

Article history:
Received 15-06-2023
Accepted 09-04-2024
Available online 21-12-2024

Keywords:
Acute lymphoblastic leukemia
Central nervous system
Chronic myeloid leukemia
CML
Lymphoid blast crisis
Paediatric

ABSTRACT

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder, characterized by BCR-ABL1 fusion resulting from t(9;22)(q34;q11) translocation. It constitutes 2% of all leukemia cases in children younger than 15 years. CML-Blast crisis (CML-BC) with extramedullary CNS involvement is a rare serious complication of CML with a poor prognosis.Lymphoid BC in CML is seen in 30% of cases.We present a case of an 8-year-old girl diagnosed with CML one year prior to presentation, who now presented with lymphoid BC with central nervous system (CNS) involvement.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by a specific cytogenetic abnormality known as the Philadelphia chromosome (Ph), which results from a reciprocal translocation between chromosomes 9 and 22, resulting in the BCR-ABL1 fusion gene. The majority of CML cases (more than 90%) are initially diagnosed in the chronic phase (CP), which is a relatively stable and indolent stage of the disease. However, a small minority of cases (approximately 2.2%) may present with de novo blast crisis (BC), which is a more aggressive and advanced stage of the disease.[1] The progression of CML from the CP to BC is characterized by the acquisition of additional chromosomal abnormalities beyond the Ph. This is primarily driven by the ongoing activity of the BCR-ABL1 fusion gene, which leads to genomic instability and the accumulation of these additional chromosomal abnormalities. As a result, the transition from CP to BC is associated with a more severe and rapidly progressing form of the disease, often requiring more intensive treatment approaches.[1]

CML in the pediatric age group is rare, constituting 2% of all leukemia cases in children younger than 15 years, with an incidence of <0.1 cases per 100,000 children.[2,3] Similar to adults, the characteristic reciprocal translocation t(9;22)(q34;q11.2), leads to the formation of BCR-ABL fusion gene product, which in turn triggers constitutive activation of tyrosine kinase signal transduction pathway.

According to WHO HAEM5 2022, CML phases are consolidated into chronic and blast phases.[3] "BC is defined by ≥20% myeloid blasts in the blood or bone marrow; or the presence of an extramedullary proliferation of blasts; or the presence of increased lymphoblasts in peripheral blood or bone marrow."[4] In CML-BC, myeloid blasts are seen in 60-80% of cases, while lymphoblasts (usually B-cell origin) are seen in 20-30% of cases resulting in acute myeloblastic leukemia (AML) and acute lymphoblastic leukemia (ALL), respectively.[5,6]

Patients with B-cell lymphoid BC often present with symptoms resembling acute leukemia, such as bleeding tendencies, bone pain, night sweats, weight loss, and fatigue. As a result, the initial evaluation should encompass

* *Corresponding author*.
E-mail address: heer20ravi@gmail.com (R. S. Heer).

https://doi.org/10.18231/j.pjms.2024.157

a range of diagnostic tests, including complete blood counts, a comprehensive metabolic panel, bone marrow aspiration and biopsy, flow cytometry, immunohistochemistry, and cytogenetic analysis.[1]

Distinguishing between CML with a lymphoid BC and de novo Ph+ ALL can be challenging, particularly when typical morphological features of CML are not evident. However, making this distinction is crucial due to its significant implications for treatment.[1] In Ph(+)B-cell ALL, the cell of origin is typically a pre-B-cell, whereas in blast-phase CML, it originates from a granulocyte-macrophage progenitor.[1] Fluorescence in-situ hybridization (FISH) plays a valuable role in identifying specific isoforms of the BCR-ABL oncogene, offering vital diagnostic rules. The p120 isoform is more frequently associated with CML, while the p190 isoform is predominantly observed in Ph(+)ALL.[1]

Extramedullary involvement in CML is rare, with CNS involvement being extremely rare.[6]The patients in these cases present with clinical features of neurological involvement like headache, cognitive changes, increased intracranial pressure, and visual disturbances.

Here, we report a case of pediatric CML in BC with CNS involvement.

2. Case Report

An eight-year-old girl presented with complaints of headache, vomiting, and low-grade fever, on and off for 1.5 months, and loss of vision in the right eye for 3 days. The patient was diagnosed as CML, (BCR-ABL1, transcript-positive) one year prior to presentation and was on treatment with imatinib. She was doing well 1.5 months before the presentation, when she started having headaches, was admitted to a local hospital, and was finally referred to our hospital. On examination, she had neck rigidity with positive Kernig's and Brudzinski's signs, bilateral lateral rectal palsy, and hepatomegaly. A routine hemogram revealed bicytopenia (hemoglobin-75g/L and leucopenia-2.9x10^9/L) and normal platelet count (2.03 x 10^9/L). Differential leucocyte count in peripheral blood smear revealed an increase in blasts (14%). The blasts were 12-16 microns in size, having a high nuclear/cytoplasmic ratio, irregular nuclear margins, immature chromatin, 1-2 conspicuous nucleoli, and a scant to moderate amount of basophilic cytoplasm. No Auer rod or granules were seen.

Under all aseptic precautions, bone marrow aspiration (BMA) was carried out. BM examination revealed solidly cellular marrow with depressed trilineage hematopoiesis and sheets of blasts up to 90%, which were negative for Myeloperoxidase (MPO) and Periodic Acid Schiff (PAS). Immunophenotyping by flow cytometry (FCM) was performed which showed 89% of cells gated in the blast region to be CD45 negative to dim positive with moderate expression of CD10, dim to moderate expression of CD22, dim expression of CD19, CD20, CD38, cCD79a, and HLA-DR. CD34 and TdT were negative. Thus, in correlation with bone marrow findings, she was diagnosed with CML in a BC.

Magnetic resonance imaging (MRI) of the brain was done, which was suggestive of meningitis with the possibility of encephalitis. In addition, kinking of the bilateral optic nerve was seen, resulting in right eye blindness and chronic papilledema. Thus, ophthalmology and neurology consultations were done for the same. Cerebrospinal fluid (CSF) analysis showed decreased glucose levels (20mg/dl) and increased protein levels (144mg/dl), suggesting meningitis. In addition, CSF malignant cytology showed numerous blasts with morphology similar to those in the peripheral blood and bone marrow. The final diagnosis was CML in BC with CNS involvement. She was started on dasatinib. Biweekly Triple intrathecal therapy (TIT) was advised, however, due to financial constraints, the parents took discharge against medical advice.

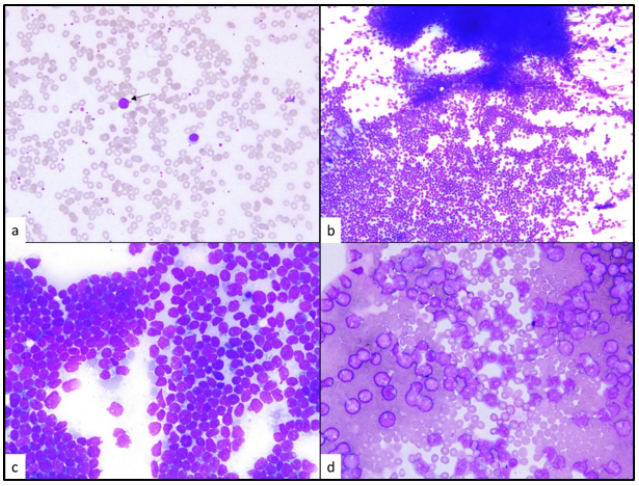

Figure 1: a: Peripheral blood smear show blast(arrow), Leishman stain, 400X; **b:** Hypercellular bone marrow aspirate showing sheets of blasts, May Grunwald Giemsa stain, 400X; **c:** Bone marrow aspirate showing sheets of blasts, May Grunwald Giemsa stain, 1000X; **d:** Haemorrhagic cellular CSF smear showing many blasts, May Grunwald Giemsa stain, 400X.

3. Discussion

Pediatric CML is a malignant condition characterized by abnormal proliferation of pluripotent stem cells, leading to granulocytic hyperplasia.[7] Pediatric CML is rare, constituting 2-3% of childhood leukemias. These cases have a higher mean elevated white blood cell (WBC) count, more pronounced splenomegaly, and aggressive disease progression in comparison to adult CML. This aggressive clinical behavior seems to arise from the genomic differences between the two. Pediatric CML

cases harbor a bimodal distribution of breakpoint cluster regions which are similar to those seen in adult Ph+ acute lymphoblastic leukemia with M-BCR rearrangement. In adult CML, a single breakpoint cluster is located within the initial 1.5 kilobases of the BCR gene.[8]

Most pediatric CML cases are in the chronic phase, and progression to BC is rare in the first three years following diagnosis.[7] Our patient presented with CML in B-lymphoid BC in the second year of diagnosis. Few studies have reported that headache and vomiting are common presenting symptoms of CNS involvement in CML, and both of these symptoms were observed in our patients as well.[9,10] According to Boudiaf et al, the first manifestation that was observed and attributed to CNS infiltration in CML-BC, was a chronic, benign headache due to cerebral edema. Similar findings were observed in our case.[7] CNS BC typically presents with clinical and radiological features of encephalitis and/or meningitis.[8] Our patient had similar findings. Extramedullary BC in CML commonly involves the lymph nodes, skin, soft tissues, bone, and spleen. However, isolated CNS BC is rare, reported occasionally in adults and exceptionally in children undergoing imatinib mesylate treatment. This is due to poor CNS penetrance of the drug and its active metabolites. Thus, the CNS acts as a sanctuary site in patients undergoing prolonged Imatinib therapy despite having a complete hematologic and cytogenetic response.[8] Similarly, our patient was on imatinib treatment when she presented with symptoms of CNS involvement although she also had a BC in bone marrow. The "BCR/ABL transcript level" or "BCR/ABL" ratio detects the quantitative measurement of the fusion gene copies, which helps in determining the prognosis and response to treatment, in patients with CML.[11] In our patient, BCR/ABL fusion protein was positive. FCM immunophenotyping aids in lineage allotment in CML-BC diagnosis.[12] BMA and FCM on bone marrow aspirate in our case, were suggestive of a B-lymphoid BC, while the CSF findings confirmed extramedullary CNS involvement.

4. Conclusion

CNS involvement in lymphoid BC of CML is a rare but known complication. The diagnosis can be challenging, as symptoms such as headache and vomiting are non-specific and can be attributed to other causes. Therefore, it requires a high index of suspicion. This case is reported because of its rarity and to create awareness among clinicians for its occurrence.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Yohannan B, George B. B-lymphoid blast phase-Chronic myeloid leukemia: Current Therapeutics. *Int J Mol Sci*. 2019;23(19):11836. doi:10.3390/ijms231911836.
2. Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. *Blood*. 2016;127(4):392–9.
3. Vardiman JW, Melo JV, Baccarani M, Radich JP, Kvasnicka HM. Chronic myeloid leukemia, BCR-ABL1-positive. In: Swedlow SH, Campo E, Harris NC, Jaffe ES, Pileri SA, Stein H, editors. WHO Classification of Tumors of Hematopoietic and lymphoid tissue. Lyon: International Agency for Research on Cancer; 2017. p. 30–6.
4. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720–48.
5. Iyer P, Carey P, Brown N, Samarasinghe S. Pediatric chronic myeloid leukemia with B-cell lymphoid blast crisis at presentation. *Blood Res*. 2013;48(2):151–3.
6. Jo S, Yoo JW, Kim S, Lee JW, Im SA, Cho B, et al. Case report: First report of isolated central nervous system lymphoblastic crisis in a child with chronic myeloid leukemia on dasatinib therapy. *Front Oncol*. 2023;13:1122714. doi:10.3389/fonc.2023.1122714.
7. Boudiaf H, Ezziane K, Rouis NO, Himrane M, Hakem S, Benchabane H. Isolated blast crisis relapse in the central nervous system of a patient treated for chronic myelogenous leukemia. *Pan Afr Med J*. 2020;36:142. doi:10.11604/pamj.2020.36.142.24155.
8. Bhatta U, Regmi D. Chronic myeloid leukemia in childhood: A case report. *J Pathol Nep*. 2021;12(2):1873–5.
9. Vijayasekharan K, Chatterjee G, Ramanathan S, Narula G, Tembhare P, Subramanian PG, et al. Sudden blast phase in pediatric chronic myeloid leukemia-chronic phase with abnormal lymphoid blasts detected by flow cytometry at diagnosis: Can it be considered a warning sign. *Cytometry B Clin Cytom*. 2021;100(3):345–51.
10. Radhika N, Minakshi M, Rajesh M, Manas BR, and DKM. Central nervous system blast crisis in chronic myeloid leukemia on imatinib mesylate therapy: report of two cases. *Indian J Hematol Blood Transfus*. 2011;27(1):51–4.
11. Jin M, Xuan C, Gao J, Han R, Xu S, Wang L, et al. Chronic myeloid leukemia extramedullary blast crisis presenting as central nervous system leukemia: A case report. *Medicine (Baltimore)*. 2018;97(45):13131. doi:10.1097/MD.0000000000013131.
12. Thavaraj V, Seth R. Prophylaxis of central nervous system leukemia: a case of chronic myeloid leukemia with lymphoid blast crisis treated with imatinib mesylate. *World J Pediatr*. 2008;4(2):145–7.

Author's biography

Mintu Ann Joy, Post Graduate Student https://orcid.org/0009-0006-7312-0355

Vandana Bhatti, Associate Professor https://orcid.org/0000-0001-7696-5704

Ravneet Singh Heer, Post Graduate Resident https://orcid.org/0009-0003-4556-8054

Kripa M Mathews, Senior Resident https://orcid.org/0000-0002-6295-3953

Cite this article: Joy MA, Bhatti V, Heer RS, Mathews KM. Chronic myeloid leukemia in lymphoid blast crisis with extramedullary CNS infiltration in a pediatric patient: A case report. *Panacea J Med Sci* 2024;14(3):886-888.