

De Novo AML with BCR-ABL Mutation vs CML in Blast Crisis: A Case Report and Literature Review

Louie Anthony T. Real, MD¹; Flordeluna Z. Mesina, MD²

Background. Acute myeloid leukemia (AML) with the Philadelphia chromosome (Ph⁺ AML) is a rare and aggressive hematologic malignancy, occurring in approximately 1-2% of all AML cases. This subtype is characterized by the presence of the BCR-ABL1 fusion gene, which significantly impacts prognosis and treatment strategies. Differentiating Ph⁺ AML from chronic myeloid leukemia (CML) in blast crisis is critical due to distinct therapeutic requirements.

Case Summary. A 26-year-old Filipino male presented with a 9-day history of fever, headache, and sore throat. Initial examination revealed anemia, marked leukocytosis, and a peripheral blood smear showing predominantly blasts. Bone marrow biopsy confirmed AML with 62.1% blasts. Cytogenetic analysis identified the Philadelphia chromosome, and molecular testing revealed the BCR-ABL fusion gene. The patient received induction chemotherapy with hydroxyurea and cytarabine, followed by doxorubicin and cytarabine. Despite complications such as neutropenic enterocolitis, the patient achieved remission with a positive response to treatment.

Conclusion. Ph⁺ AML poses significant diagnostic and therapeutic challenges due to its aggressive nature and poor prognosis. Effective management requires accurate diagnosis, integration of tyrosine kinase inhibitors, and potential hematopoietic stem cell transplantation. Further research is needed to optimize treatment strategies and improve outcomes for this rare AML subtype. Personalized treatment and vigilant monitoring for relapse will enhance patient survival and quality of life.

Keywords. De Novo AML with BCR-ABL Mutation; BLAST crisis CML; Case Report; Ph⁺ AML

Introduction

Acute myeloid leukemia (AML) is a heterogeneous clonal hematopoietic malignancy characterized by the rapid growth of abnormal myeloid cells in the bone marrow and blood, interfering with the production of normal blood cells (Lagunas-Rangel et al., 2017; Redner & Kessel, 2022). The Philadelphia chromosome (Ph), resulting from a translocation between chromosomes 9 and 22, is typically associated with chronic myeloid leukemia (CML) in its blast crisis phase, a more aggressive phase characterized by an increase in blast cells (Kang et al., 2016; Soupir et al., 2007).

While rare, AML can also harbor the Philadelphia chromosome mutation (Ph⁺ AML), which occurs in approximately 1-2% of all cases (Sampaio et al., 2021). This mutation indicates a distinct molecular subtype of AML with unique clinical characteristics and therapeutic implications (DiNardo & Cortes, 2016). Differentiating Ph⁺ AML from CML in blast crisis is crucial, as these two

entities require distinct treatment approaches and carry different prognoses (Pullarkat et al., 2008).

We present a case of a 26-year-old Filipino male who initially presented with non-specific symptoms suggestive of acute leukemia. Further investigation confirmed the presence of the Philadelphia chromosome, diagnosing the patient with Ph⁺ AML. This case highlights the importance of thorough diagnostic evaluation and accurate classification of acute leukemia for appropriate management and improved patient outcomes.

Case Presentation

8 years prior to admission, during annual physical exam, A 26-year-old Filipino male without significant past medical history, nor pertinent family history of genetic diseases presented to the emergency room with a 9-day history of fever, headache, and sore throat. Physical examination revealed a weak-looking patient with dry mucosa and coarse crackles in the right basal lung fields. Initial complete blood count showed anemia (hemoglobin 11.1 g/L), marked leukocytosis (WBC 329.39) with 40% blast, and a peripheral blood smear

¹Cardinal Santos Medical Center-Department of Internal Medicine, Philippines

²Cardinal Santos Medical Center, Department of Internal Medicine, Section of Hematology

Corresponding author: Louie Anthony T. Real, MD
Email: louiedebakey@gmail.com

with increased white blood cells predominantly blasts, normocytic normochromic red blood cells, and adequate platelets. A working diagnosis of acute leukemia, likely acute myelogenous leukemia (AML), was made, and the patient was started on hydroxyurea and cytarabine.

A bone marrow biopsy report confirmed the diagnosis of Acute Myeloid Leukemia with 62.1% blasts in a markedly hypercellular marrow for the patient's age (55-95%). Additionally, bone marrow flow cytometry showed findings consistent with a small blast population lineage, with medium to large-sized blasts featuring ovoid to irregular nuclei, fine to slightly coarse chromatin, few conspicuous nucleoli, and scant to moderately abundant cytoplasm. Karyotyping revealed a 46 XY t(9;22)(q34;q11.2) / 46XY karyotype, indicating breakage and reunion at bands 9q34 and 22q11.2, and the presence of the Philadelphia chromosome in 12 out of 19 analyzed cells. The abnormal chromosome 22 produced from this reciprocal translocation is called the "Philadelphia chromosome." Fluorescence in situ hybridization (FISH) for the BCR-ABL fusion gene was positive in 53.33% of cells for t(9;22) / BCR/ABL, confirming the presence of the Philadelphia chromosome mutation. Flow cytometry revealed a small blast population lineage with CD34-positive precursor cells at 0.51% of the total events. The granulocytes were identified at 49.24% of the white cells, with mature lymphocyte cell subsets at 19.82%, consisting mostly of mature T-cells admixed with occasional natural killer cells and few mature B-cells.

He was given induction chemotherapy using a 7+3 regimen consisting of cytarabine and doxorubicin. Nadir of blood counts occurred around Day 10 with concomitant gastrointestinal tract infection. He was treated with broad-spectrum antibiotics for neutropenic enterocolitis. There was a gradual recovery of blood counts and resolution of the infection. Imatinib 100 mg/tablet, one tablet thrice daily, was added, and the patient was found to be MRD negative at Day 28. Imatinib therapy was continued following confirmation of MRD negativity.

A repeat bone marrow aspiration (BMA) was performed on Day 28 post-chemotherapy, one day prior to discharge, demonstrating a positive response to treatment with improving marrow cellularity and no residual disease detected by molecular analysis. Despite developing neutropenic enterocolitis as a complication of chemotherapy, the patient responded positively to treatment, achieving remission with a reactive and improving bone marrow. Fluorescence in situ hybridization (FISH) for the BCR-ABL fusion gene confirmed the positive response, and the patient was eventually discharged with stable hematologic parameters and no further complications.

Discussion

AML with the Philadelphia chromosome (Ph+ AML) and CML in blast crisis are both characterized by the presence of the BCR-ABL fusion gene, resulting from a

translocation between chromosomes 9 and 22 (Calabretta & Perrotti, 2004). However, they are distinct clinical entities requiring different therapeutic approaches. Ph+ AML is a rare subtype, occurring in about 1-2% of all AML cases (Abdulkarim et al., 2009). CML in blast crisis represents an advanced, aggressive phase of CML, which typically progresses from a chronic phase characterized by increased myeloid cells and basophilia (Wang et al., 2021).

Previous case reports on Ph+ AML emphasize its aggressive clinical course, poor prognosis, and the critical role of targeted therapies including tyrosine kinase inhibitors (TKIs) such as imatinib. Similar to our case, these reports underline the necessity of integrating TKIs into induction chemotherapy and considering subsequent hematopoietic stem cell transplantation (HSCT) for improved outcomes (Ahmadmehrabi et al., 2021; Saleh et al., 2022).

Patients with CML usually have a history of a chronic phase with insidious onset of symptoms such as fatigue, weight loss, and splenomegaly (Kalita, 2014). This phase can last several years before progressing to an accelerated phase and eventually a blast crisis. In contrast, Ph+ AML presents acutely with no preceding chronic phase. Patients often exhibit symptoms related to bone marrow failure, such as anemia, infection, and bleeding, due to the rapid proliferation of blasts.

In CML blast crisis, the bone marrow examination reveals a high percentage of blasts, typically greater than 20%, along with features of the preceding chronic phase, such as increased myeloid cells and basophilia (Khemka et al., 2019). Additional cytogenetic abnormalities are often present in CML blast crisis (Ali et al., 2009), reflecting disease progression and genetic instability, similar to our case. On the other hand, Ph+ AML shows a high blast count from the onset without prior myeloproliferative features. The presence of the Philadelphia chromosome in both conditions necessitates molecular studies to differentiate between them.

Distinguishing Ph+ AML from CML in blast crisis is challenging due to overlapping clinical and molecular features. Accurate diagnosis relies on clinical history, bone marrow examination, cytogenetic analysis, and molecular studies (Pullarkat et al., 2008; Senapati et al., 2023). Misclassification can lead to inappropriate treatment, adversely affecting patient outcomes, as seen in our patient.

Clinical History: Careful documentation of the patient's medical history is crucial. The absence of a chronic phase or myeloproliferative features supports a diagnosis of Ph+ AML.

Bone Marrow Examination: Identifying specific features, such as the percentage of blasts and the presence of prior myeloproliferative changes, helps in differentiation.

Cytogenetic and Molecular Studies: For accurate classification, detailed analysis of chromosomal abnormalities and the presence of the BCR-ABL1 fusion

gene and other genetic markers is essential (Senapati et al., 2023).

The Philadelphia chromosome in AML signifies a distinct and aggressive molecular subtype with unique clinical characteristics and therapeutic challenges. Ph+ AML is associated with a poorer prognosis compared to Ph-negative AML, with lower overall survival rates and higher relapse rates despite aggressive treatment (Tran & Tasian, 2021). The BCR-ABL1 fusion gene is a potent oncogenic driver, promoting increased proliferation and survival of leukemic cells (Zhou et al., 2018).

The conventional treatment for AML typically involves induction chemotherapy aimed at achieving complete remission (CR) by eradicating the majority of leukemic cells. This is often accomplished using a combination of cytarabine and an anthracycline, such as daunorubicin or idarubicin (De Kouchkovsky & Abdul-Hay, 2016). Induction therapy is followed by post-remission or consolidation therapy, which aims to eliminate residual leukemic cells and prevent relapse (Hamadani & Awan, 2010). Consolidation therapy may include additional cycles of intensive chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT), or autologous HSCT (Sun et al., 2015), depending on individual patient risk factors and response to initial treatment.

For AML patients with the Philadelphia chromosome (Ph+ AML), the incorporation of tyrosine kinase inhibitors (TKIs) that target the BCR-ABL1 oncoprotein, such as imatinib, dasatinib, and nilotinib, has significantly improved treatment outcomes (Saleh et al., 2022), similar to our case. These TKIs are often combined with conventional chemotherapy during induction and consolidation phases to enhance response rates and overall survival. Although the optimal use of TKIs in de novo Ph+ AML is still under investigation, early integration into treatment regimens has shown promise in improving prognosis and achieving remission (Ahmadmehrabi et al., 2021), as seen in our patient.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment option for Ph+ AML, particularly in younger patients with suitable donors (Algeri et al., 2021), like our case. HSCT replaces the patient's leukemic bone marrow with healthy stem cells, offering the potential for long-term remission and a graft-versus-leukemia effect. However, HSCT has significant risks, including graft-versus-host disease and treatment-related mortality. It is generally reserved for patients who achieve complete remission following initial chemotherapy and TKI therapy (Csanadi et al., 2019; Greinix et al., 2022).

Close follow-up and monitoring for relapse are essential for early detection and intervention in Ph+ AML patients. This typically involves regular blood tests, bone marrow examinations, and molecular testing to assess for minimal residual disease (MRD) (Pfeifer et al., 2012). Ongoing monitoring allows for timely adjustments in treatment, potentially improving long-term outcomes. The importance of vigilant follow-up cannot be

overstated, as early identification of relapse can lead to prompt treatment interventions, thereby enhancing the chances of achieving sustained remission and improved survival (Tsirigotis et al., 2016).

Conclusion

AML with the Philadelphia chromosome (Ph+ AML) is a rare and complex disease requiring careful differentiation from chronic myeloid leukemia (CML) in blast crisis to ensure appropriate management. This case underscores the necessity of timely diagnosis, aggressive treatment, and vigilant follow-up to improve patient outcomes despite the aggressive nature and high relapse risk associated with Ph+ AML. Further research is essential to optimize treatment strategies and improve long-term survival rates for this challenging subtype.

References

1. Abdulkarim, K., Girodon, F., Johansson, P., Maynadié, M., Kutti, J., Carli, P. M., Bovet, E., & Andréasson, B. (2009). AML transformation in 56 patients with Ph- MPD in two well defined populations. *European journal of haematology*, 82(2), 106-111.
2. Ahmadmehrabi, K., Haque, A. R., Aleem, A., Griffiths, E. A., & Roloff, G. W. (2021). Targeted therapies for the evolving molecular landscape of acute myeloid leukemia. *Cancers*, 13(18), 4646.
3. Algeri, M., Merli, P., Locatelli, F., & Pagliara, D. (2021). The role of allogeneic hematopoietic stem cell transplantation in pediatric leukemia. *Journal of clinical medicine*, 10(17), 3790.
4. Ali, R., Ozkalemkas, F., Ozkocaman, V., Yakut, T., Nazlioglu, H. O., Budak, F., Pekgoz, M., Korkmaz, S., Karkucak, M., & Ozelik, T. (2009). Sudden blastic crisis and additional chromosomal abnormalities during chronic myeloid leukemia in the imatinib era. *International journal of clinical oncology*, 14, 545-550.
5. Calabretta, B., & Perrotti, D. (2004). The biology of CML blast crisis. *blood*, 103(11), 4010-4022.
6. Csanadi, M., Agh, T., Tordai, A., Webb, T., Jeyakumaran, D., Sengupta, N., Schain, F., & Mattsson, J. (2019). A systematic literature review of incidence, mortality, and relapse of patients diagnosed with chronic graft versus host disease. *Expert review of hematology*, 12(5), 311-323.
7. De Kouchkovsky, I., & Abdul-Hay, M. (2016). Acute myeloid leukemia: a comprehensive review and 2016 update. *Blood cancer journal*, 6(7), e441-e441.
8. DiNardo, C. D., & Cortes, J. E. (2016). Mutations in AML: prognostic and therapeutic implications. *Hematology 2014, the American Society of Hematology Education Program Book*, 2016(1), 348-355.
9. Greinix, H. T., Eikema, D.-J., Koster, L., Penack, O., Yakoub-Agha, I., Montoto, S., Chabannon, C.,

- Styczynski, J., Nagler, A., & Robin, M. (2022). Improved outcome of patients with graft-versus-host disease after allogeneic hematopoietic cell transplantation for hematologic malignancies over time: an EBMT mega-file study. *haematologica*, 107(5), 1054.
10. Hamadani, M., & Awan, F. T. (2010). Remission induction, consolidation and novel agents in development for adults with acute myeloid leukaemia. *Hematological Oncology*, 28(1), 3-12.
 11. Illangeswaran, R. S. S., Das, S., Paul, D. Z., Mathews, V., & Balasubramanian, P. (2019). A personalized approach to acute myeloid leukemia therapy: current options. *Pharmacogenomics and personalized medicine*, 167-179.
 12. Kalita, A. (2014). *Clinico-Hematological Study of Chronic Myeloid Leukemia* Rajiv Gandhi University of Health Sciences (India)].
 13. Kang, Z.-J., Liu, Y.-F., Xu, L.-Z., Long, Z.-J., Huang, D., Yang, Y., Liu, B., Feng, J.-X., Pan, Y.-J., & Yan, J.-S. (2016). The Philadelphia chromosome in leukemogenesis. *Chinese journal of cancer*, 35, 1-15.
 14. Khemka, R., Gupta, M., & Jena, N. K. (2019). CML with megakaryocytic blast crisis: Report of 3 cases. *Pathology & Oncology Research*, 25, 1253-1258.
 15. Lagunas-Rangel, F. A., Chávez-Valencia, V., Gómez-Guijosa, M. Á., & Cortes-Penagos, C. (2017). Acute myeloid leukemia—genetic alterations and their clinical prognosis. *International Journal of Hematology-Oncology and Stem Cell Research*, 11(4), 328.
 16. Pemovska, T., Kontro, M., Yadav, B., Edgren, H., Eldfors, S., Szwajda, A., Almusa, H., Bespalov, M. M., Ellonen, P., & Ellonen, E. (2013). Individualized systems medicine strategy to tailor treatments for patients with chemorefractory acute myeloid leukemia. *Cancer discovery*, 3(12), 1416-1429.
 17. Pfeifer, H., Wettner, C., Wassmann, B., Giagounidis, A., Stelljes, M., Dührsen, U., Schmalzing, M., Schaich, M., De Wit, M., & Ganser, A. (2012). Long term follow up of elderly patients with philadelphiapositive acute lymphoblastic leukaemia (PH+ ALL): Updated results of the GMALL elderly trials. *haematologica*, 97, 463.
 18. Pullarkat, S. T., Vardiman, J. W., Slovak, M. L., Rao, D. S., Rao, N. P., Bedell, V., & Said, J. W. (2008). Megakaryocytic blast crisis as a presenting manifestation of chronic myeloid leukemia. *Leukemia Research*, 32(11), 1770-1775.
 19. Redner, A., & Kessel, R. (2022). Acute myeloid leukemia. In *Lanzkowsky's Manual of Pediatric Hematology and Oncology* (pp. 439-458). Elsevier.
 20. Saleh, K., Fernandez, A., & Pasquier, F. (2022). Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia in adults. *Cancers*, 14(7), 1805.
 21. Sampaio, M. M., Santos, M. L. C., Marques, H. S., de Souza Gonçalves, V. L., Araújo, G. R. L., Lopes, L. W., Apolonio, J. S., Silva, C. S., de Sá Santos, L. K., & Cuzzuol, B. R. (2021). Chronic myeloid leukemia—from the Philadelphia chromosome to specific target drugs: A literature review. *World journal of clinical oncology*, 12(2), 69.
 22. Senapati, J., Jabbour, E., Kantarjian, H., & Short, N. J. (2023). Pathogenesis and management of accelerated and blast phases of chronic myeloid leukemia. *Leukemia*, 37(1), 5-17.
 23. Soupir, C. P., Vergilio, J.-A., Cin, P. D., Muzikansky, A., Kantarjian, H., Jones, D., & Hasserjian, R. P. (2007). Philadelphia chromosome-positive acute myeloid leukemia: a rare aggressive leukemia with clinicopathologic features distinct from chronic myeloid leukemia in myeloid blast crisis. *American journal of clinical pathology*, 127(4), 642-650.
 24. Sun, Y., Wang, J., Jiang, Q., Xu, L., Liu, D., Zhang, X., Liu, K., & Huang, X. (2015). Haploidentical hematopoietic SCT may be superior to conventional consolidation/maintenance chemotherapy as post-remission therapy for high-risk adult ALL. *Bone marrow transplantation*, 50(1), 20-25.
 25. Tran, T. H., & Tasian, S. K. (2021). Has Ph-like ALL superseded Ph+ ALL as the least favorable subtype? *Best Practice & Research Clinical Haematology*, 34(4), 101331.
 26. Tsirigotis, P., Byrne, M., Schmid, C., Baron, F., Ciceri, F., Esteve, J., Gorin, N., Giebel, S., Mohty, M., & Savani, B. (2016). Relapse of AML after hematopoietic stem cell transplantation: methods of monitoring and preventive strategies. A review from the ALWP of the EBMT. *Bone marrow transplantation*, 51(11), 1431-1438.
 27. Wang, L., Li, L., Chen, R., Huang, X., & Ye, X. (2021). Understanding and monitoring chronic myeloid leukemia blast crisis: how to better manage patients. *Cancer Management and Research*, 4987-5000.
 28. Zhou, T., Medeiros, L. J., & Hu, S. (2018). Chronic myeloid leukemia: beyond BCR-ABL1. *Current hematologic malignancy reports*, 13, 435-445.