



Secondary Acute Myeloid Leukemia in a Chronic Myeloid Leukemia Patient in Deep Molecular Response—An Unusual Case Report

Gorantala Bharathi Devi¹ Perumal Kalaiyarasi Jayachandran¹ Jhansi Rani Arumugam²
Karthik Bommanna² Shirley Sundersingh²

¹Department of Medical Oncology, Cancer Institute (WIA), Adyar, Chennai, Tamil Nadu, India

²Department of Hematopathology, Cancer Institute (WIA), Adyar, Chennai, Tamil Nadu, India

Address for correspondence Dr. Perumal Kalaiyarasi Jayachandran, MD, MRCP (UK), DM, Department of Medical Oncology, Cancer Institute (WIA), 38, Sardar Patel Road, Guindy, Chennai, Tamil Nadu 600036, India (e-mail: dr.pkjayachandran@gmail.com).

South Asian J Cancer 2022;11(2):175–177.

Abstract



Perumal Kalaiyarasi Jayachandran

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder that develops from the stem cell compartment. The classical translocation (*BCR-ABL1*) is present in approximately 95% of CML patients. Through disease progression, clonal evolution with additional chromosomal abnormalities (ACAs) start appearing. Although relatively rare, chromosomal abnormalities can exist or develop in the Philadelphia (Ph)-negative clones, which may lead to the evolution of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). We hereby present a case of AML which emerged from a Ph-negative clone in a patient with a history of CML who was in deep molecular response. The possible mechanisms of ACAs have been discussed.

Keywords

- ▶ AML in CML
- ▶ secondary AML
- ▶ additional chromosomal abnormalities in Ph-negative clone
- ▶ clonal evolution
- ▶ secondary clone

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative hematologic disorder that develops from aberrancy in the stem cell compartment. The hallmark of CML is the presence of Philadelphia (Ph) chromosome which is an abnormally

smaller 22nd chromosome formed due to an unbalanced translocation between the Abelson (*ABL1*) gene in the long arm of 9th chromosome and the breakpoint cluster region (*BCR*) gene in the long arm of the 22nd chromosome (t(9;22)(q34;q11)). This classical translocation (*BCR-ABL1*) is present in approximately 95% of CML patients.¹ Over time, when the

DOI <https://doi.org/10.1055/s-0041-1739178> ISSN 2278-330X

How to cite this article: Devi GB, Jayachandran PK, Arumugam JR, et al. Secondary Acute Myeloid Leukemia in a Chronic Myeloid Leukemia Patient in Deep Molecular Response—An Unusual Case Report South Asian J Cancer 2022;11(2):175–177.

© 2022. MedIntel Services Pvt Ltd. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

disease progression happens, clonal evolution with additional chromosomal abnormalities (ACAs) emerge.² ACAs are seen in approximately 30% of cases in the accelerated phase and 50 to 80% of cases in the blast phase. Common ACAs are trisomy of chromosome 8, an extra copy of the Ph-chromosome, isochromosome of 17q, and trisomy of chromosome 19.³ Although relatively rare, chromosomal abnormalities can exist or develop in the Ph-negative clones, which may lead to the development of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

We present a case of AML that had emerged from a Ph-negative clone in a patient with a history of CML who was in deep molecular response and have discussed the potential mechanisms of the chromosomal abnormalities in Ph-negative cells.

Case Presentation

A 59-year-old female presented to us with complaints of loss of appetite and weight. She was found to have massive splenomegaly and leukocytosis and was diagnosed as Ph-positive CML. Conventional cytogenetics showed t(9;22) (q34;q11.2). Fluorescence in situ hybridization (FISH) for *BCR-ABL1* was positive. The *BCR-ABL1* qualitative polymerase chain reaction (PCR) showed an e14a2 transcript. She was started on Imatinib 400 mg once daily. She achieved complete hematological response (CHR) and major molecular response (MMR) at 2 months and 6 months, respectively. She was compliant with the drug and was on regular follow-up with regular monitoring by real-time polymerase chain reaction PCR (RT-PCR) with international standardization (IS). After 3.5 years of imatinib therapy, she presented to us with thrombocytopenia. Her hemoglobin, white cell count, and platelet counts were 9.7 g/dl, 2500 cells/mm³ and 60000 cells/mm³, respectively. She did not have any lymphadenopathy or hepatosplenomegaly. She did not have any preceding history of a viral illness. Bone marrow aspiration showed an abnormal blast population of 25%. Immunophenotyping analysis by flow cytometry showed that the blast population was abnormal with the expression of CD13, CD34, CD38, CD58, CD123, HLA-DR, and CD117. Conventional cytogenetics showed trisomy of the 8th chromosome with the absence of a Ph chromosome in all the 20 metaphases. FISH for *BCR-ABL1* on bone marrow aspirate was negative. RT-PCR showed a ratio of *BCR-ABL1/ABL1* of 0.005% (IS). Hence, she was diagnosed as secondary AML with CML in deep molecular response. She was given decitabine-based induction with the continuation of imatinib. At the end of four cycles of decitabine, bone marrow evaluation did not show any response with 44% blasts. She was offered an option of intensive induction chemotherapy with cytarabine and daunorubicin. She denied further treatment and opted for oral palliative therapy. She did not come back for a follow-up.

Discussion

Despite available literature, the exact mechanisms which lead to the development of ACAs in Ph-negative cells are not completely understood. One possible mechanism is that tyrosine kinase inhibitors (TKI) used in the treatment, which can cause chromosomal changes in Ph-negative cells by the inhibition of cellular ABL kinase (c-ABL) activity. c-ABL has an important role in the DNA repair mechanism.⁴ On the inhibition of c-ABL activity, susceptibility to DNA damage increases which, in turn, leads to chromosomal abnormalities.

The next possible mechanism is that the pathogenesis of CML is a multiple-step process, in which the primary translocation involving chromosome 9 and 22 is not the earliest event. It rather originates from a Ph-negative hematopoietic stem cell clone. The genetic abnormality in the early Ph-negative clone governs the development of t(9;22) and also other ACAs. The emergence of t(9;22), leads to the production of *BCR-ABL1* kinase, which is a potent activator of the growth of the Ph-positive clone which, in turn, leads to masking of the cells with other chromosomal changes. On the use of targeted therapy, Ph-positive cells are suppressed and eliminated and hence there is the reemergence of Ph negative cells with ACAs.⁵⁻⁸

There was a report of a high frequency of somatic mutations in genes that were associated with myeloid disorders in Ph-negative cells of CML patients treated with TKI.⁸ A report from the pre-TKI era suggested that multiple events were required for leukemogenesis in CML.⁹ The early genetic abnormality that cooperates with *BCR-ABL1* could also cooperate with other genetic aberrations, which may lead to the development of AML. Thus, an early genetic clone could predispose to both the leukemias. Alternatively, abnormal marrow stroma in some CML patients may influence both the acquirement of *BCR-ABL1* and other genetic mutations without *BCR-ABL1*, which may lead to MDS or AML.¹⁰

To conclude, CML has very complex pathogenesis during evolution and also during treatment. ACAs can be associated with both Ph-positive clones and also Ph-negative clones. Patients with ACAs in Ph clones are more likely to become nonresponsive and also highly likely to progress to the next phase. If an ACA is identified in Ph-negative clone, such patients might be candidates for closer follow-up for looking for the development of secondary MDS and AML.

Funding

There were no external sources of funding for this project.

Conflict of Interest

None of the authors have any relevant conflicts of interest to declare.

References

- 1 Champlin RE, Golde DW. Chronic myelogenous leukemia: recent advances. *Blood* 1985;65(05):1039–1047
- 2 Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood* 2013;122(06):872–884
- 3 Jabbour E, Kantarjian HM, Abruzzo LV, et al. Chromosomal abnormalities in Philadelphia chromosome negative metaphases appearing during imatinib mesylate therapy in patients with newly diagnosed chronic myeloid leukemia in chronic phase. *Blood* 2007;110(08):2991–2995
- 4 Wang X, Zeng L, Wang J, et al. A positive role for c-Abl in Atm and Atr activation in DNA damage response. *Cell Death Differ* 2011;18(01):5–15
- 5 Bumm T, Müller C, Al-Ali H-K, et al. Emergence of clonal cytogenetic abnormalities in Ph- cells in some CML patients in cytogenetic remission to imatinib but restoration of polyclonal hematopoiesis in the majority. *Blood* 2003;101(05):1941–1949
- 6 Terre C, Eclache V, Rousselot P, et al; France Intergroupe pour la Leucemie Myeloide Chronique. Report of 34 patients with clonal chromosomal abnormalities in Philadelphia-negative cells during imatinib treatment of Philadelphia-positive chronic myeloid leukemia. *Leukemia* 2004;18(08):1340–1346
- 7 Kovitz C, Kantarjian H, Garcia-Manero G, Abruzzo LV, Cortes J. Myelodysplastic syndromes and acute leukemia developing after imatinib mesylate therapy for chronic myeloid leukemia. *Blood* 2006;108(08):2811–2813
- 8 Schmidt M, Rinke J, Schäfer V, et al. Molecular-defined clonal evolution in patients with chronic myeloid leukemia independent of the BCR-ABL status. *Leukemia* 2014;28(12):2292–2299
- 9 Deininger MWN, Cortes J, Paquette R, et al. The prognosis for patients with chronic myeloid leukemia who have clonal cytogenetic abnormalities in Philadelphia chromosome-negative cells. *Cancer* 2007;110(07):1509–1519
- 10 Bhatia R, McClave PB, Dewald GW, Blazar BR, Verfaillie CM. Abnormal function of the bone marrow microenvironment in chronic myelogenous leukemia: role of malignant stromal macrophages. *Blood* 1995;85(12):3636–3645