Leena Rawal et al. JBC Genetics. 2025;8(2):106-109
DOI: 10.24911/JBCGenetics.11-2362

CASE REPORT

A novel five-way complex translocation t(9;10;15;21;22)(q34;p11.2;q22;q22;q11.2) in a Chronic myeloid leukemia patient

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ABSTRACT

Background: The *BCR*::*ABL1* gene fusion is the hallmark of chronic myeloid leukemia (CML). Variant Philadelphia chromosome (Ph)-positive cases with complex chromosomal rearrangements involving additional chromosomes occur in 4-11% of cases, but their prognostic significance remains unclear.

Methods: A 20-year-old male presenting with leukocytosis and anemia was evaluated using conventional cytogenetics, fluorescence *in situ* hybridization (FISH), and reverse transcription PCR (RT-PCR) to identify chromosomal abnormalities and *BCR*::*ABL1* transcript type.

Results: Cytogenetic analysis revealed a novel balanced five-way translocation: 46,XY,t(9;10;15;21;22)(q34;p11.2;q22;q22;q11.2). FISH confirmed the *BCR*::*ABL1* fusion in 97% of nuclei, and RT-PCR detected the e13a2 (p210) *BCR*::*ABL1* transcript. The patient exhibited rapid progression to blast crisis and resistance to first-line imatinib therapy.

Conclusion: This novel five-way translocation in Ph-positive CML highlights the importance of comprehensive cytogenetic and molecular characterization to detect rare variants that may influence treatment response and prognosis.

Keywords: Chronic myeloid leukemia (CML), *BCR::ABL1* fusion, Philadelphia chromosome, five-way translocation, cytogenetics.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that arises from abnormal pluripotent bone marrow stem cells characterized by uncontrolled proliferation of myeloid lineage cells. It is consistently associated with the fusion gene, *BCR*::*ABL1*, which is located in the Philadelphia (Ph) chromosome with the characteristic t(9;22)(q34;q11.2) translocation. The Philadelphia chromosome, a small derivative of chromosome 22, arises from transposition of the 3′ *ABL1* region (9q34) to the 5′ *BCR* region (22q11.2) thereby forming an oncogenic *BCR*::*ABL1* gene fusion product. This chimeric gene product yields an abnormal tyrosine kinase that dysregulates several signaling pathways involved in cell cycle control and apoptosis (1). CML patients usually present with leukocytosis and increased platelets in the peripheral blood, with bone marrow showing myeloid hyperplasia, and an elevated myeloid to erythroid ratio (M:E Ratio). The drug imatinib mesylate also known as Gleevec or Glivec, is commonly used as the first-line oral tyrosine kinase inhibitor (TKI) targeting the *BCR*::*ABL1* and PDGFR kinase activity, promoting apoptosis and inhibiting proliferation of leukemic cells in CML and Acute lymphoblastic leukemia (ALL) (2). The patients treated with imatinib have been reported to experience an improved quality of life. However, resistance to imatinib remains to be a challenging obstacle for better clinical outcome (3). The presence of the Ph chromosome has been

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Received: 12 September 2025 | **Revised:** 25 October 2025 | **Accepted:** 11 December 2025

observed in ~90% of patients diagnosed with CML, while a small subset, 4-11% of patients exhibit complex variant translocations which is an outcome of involvement of one or more chromosomes other than 9 and 22 (4). Here, we present a case of CML with a novel five-way chromosomal rearrangement, exhibiting resistance to TKI therapy.

Case Presentation

A 20-year-old male presented with a clinical history of leukocytosis and anemia. The hematological parameters detected hemoglobin 6.7 gm/dl, platelet count 590.00 × 10^3/c.mm, and white blood cell count of 191.30 × 10^3/c.mm with a differential count of 4% blasts, 27% myelocytes, 9% metamyelocytes, 52% band neutrophils, 3% basophils, 2% erythroid series, 1% lymphocytes, and 2% monocytes. Subsequent bone marrow biopsy and aspirate smears revealed a hypercellular marrow (95%) with a predominance of immature myeloid cells, mature neutrophils and no apparent increase of blasts. Additionally, there was an increase in megakaryocytes with few dwarf forms and occasional normoblasts seen in erythroid elements. The patient was diagnosed with CML in chronic phase and then initiated treatment with imatinib at 400 mg/day orally. Following imatinib initiation (400 mg/day), the patient achieved only a transient hematologic response. Within six months, leukocytosis and circulating blasts reappeared, consistent with disease progression. The patient entered blast crisis approximately eight months after diagnosis. A second-line tyrosine kinase inhibitor, dasatinib, was introduced but failed to achieve hematologic remission. Despite supportive management, the disease continued to progress, and the patient succumbed to complications of blast crisis about one year after initial presentation.

Methods

Conventional cytogenetics

Bone marrow specimens were collected and cultured in RPMI-1640 medium supplemented with Fetal Bovine Serum. After overnight incubation, harvesting, washing, slide preparation and GTG banding was performed according to standard protocol (5). Twenty well-spread and banded metaphases were analyzed and metaphases were captured in Cytovision image analysis and capturing system version 7.7. Karyotyping nomenclature was assigned in accordance with International System of Cytogenetic Nomenclature (ISCN) 2024 guidelines (6).

Molecular cytogenetics (FISH)

FISH was performed using Dual Color Dual Fusion *BCR::ABL1* locus specific identifier (LSI) probe, according to manufacturer's (Zytovision) instructions. Images were captured using an Epi-fluorescence microscope (AXIO Imager.Z2, Zeiss, USA), and analysis was performed with ISIS software (Metasystems, Germany).

Result

G-banded karyotyping revealed a balanced reciprocal five-way translocation involving chromosomes 9q34, 10p11.2, 15q22, 21q22, and 22q11.2 in all 20 analyzed metaphases, with Karyotype: 46,XY,t(9;10;15;21;22)(q34;p11.2;q22;q22;q11.2) (Figure 1A). FISH confirmed a single *BCR::ABL1* fusion signals in 97% of nuclei (2R2G1F); ISCN: nuc ish (ABL1x3),(BCRx3),(ABL1 con BCRx1)[194/200] (Figure 1B). The p210 *BCR/ABL1* mRNA transcript (e13a2 transcript) was detected through RT-PCR. Sequencing of the *BCR::ABL1* kinase domain at the time of imatinib resistance did not identify any known mutations associated with TKI resistance.

Discussion

Chronic myeloid leukemia (CML) is primarily caused by a balanced translocation between the long arms of chromosomes 9 and 22, and less commonly by variant or complex translocations. The primary pathogenic event in CML is the constitutive activation of the *ABL1* tyrosine kinase which is usual molecular event underlying

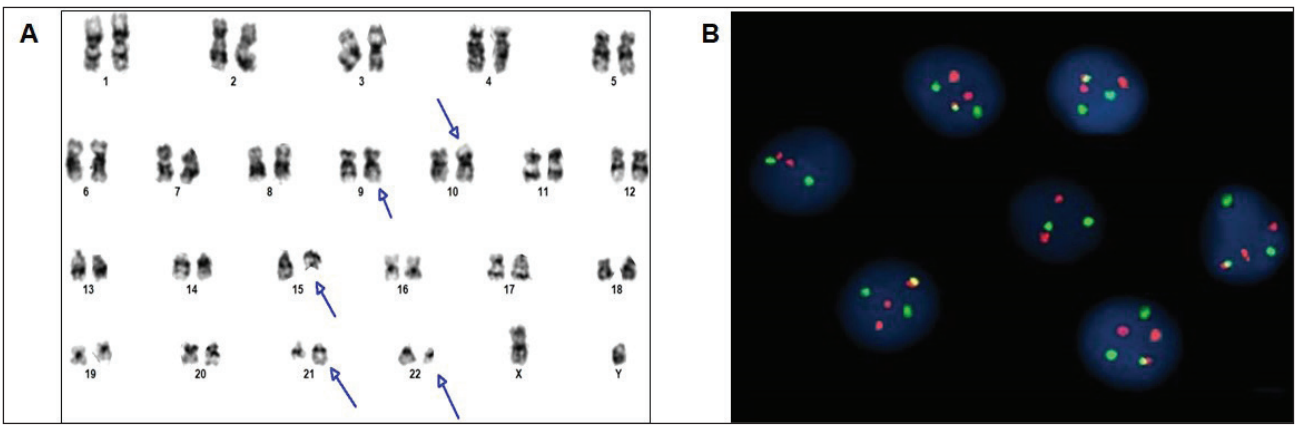

Figure 1. *CML patient karyotype, 46,XY,t(9;10;15;21;22)(q34;p11.2;q22;q22;q11.2), a five-way translocation, showing the involvement of chromosomes 9, 10, 15, 21 and 22 in the translocation process. The translocated regions on the respective derivative chromosomes are depicted by arrows (blue) (A). FISH on interphase nuclei using BCR::ABL1 dual fusion probe: The BCR locus on chromosome 22 is indicated in green and ABL1 locus on chromosome 9 is shown with orange. The yellow fusion signal is indicative of the fusion gene BCR::ABL1 (B).*

classical, cryptic and variant Philadelphia chromosome (Ph) translocations. Variant chromosomal abnormalities in Ph-positive cells can occur either as primary or secondary events. Complex chromosomal abnormalities have been reported in 4-11% of the CML cases (4). However, 5-way translocation is a rare event.

In our case, chromosomes 9, 10, 15, 21, and 22 were involved in a complex translocation including the Ph chromosome. To the best of our knowledge, this is the first reported case with this specific five-way translocation. According to the literature, only 12 cases with 5-way translocation in patients with CML have been reported (7). Owing to the rarity of the variant Ph chromosome in CML patients, the mechanism underlying such rearrangements remains unclear. Two mechanisms have been proposed: (i) a one-step mechanism in which chromosome breakage occurs simultaneously on 3, 4, or 5 different chromosomes in 3-way, 4-way, or 5-way translocation, respectively, and (ii) a two-step mechanism involving two consecutive translocations in which a standard t(9;22) translocation is followed by a second translocation involving additional chromosomes (8). These mechanisms may have prognostic relevance, as a single-step rearrangement may confer a prognosis similar to classical Ph translocations, whereas a multi-step mechanism suggests clonal evolution associated with an unfavorable prognosis.

In the present study, it is likely that first-step, a primary translocation t(9;22) generating the *BCR*::*ABL1* chimeric fusion, secondary rearrangements leading to the five-way translocation involving chromosomes 10, 15, 21, and 22, and the derivative chromosome 9 (Figure 2). Few studies have reported the poor progression of patient with Ph-positive CML cases with five-way translocations (7,9). Lau *et al*. reported a CML patient with a five-way translocation, t(9;22;10;12;1) who experienced multiple relapses and ultimately succumbed to sepsis (10). Another CML patient with 5-way translocation was reported to have t(3;4;9;11;22) and later died in the chronic state (11).

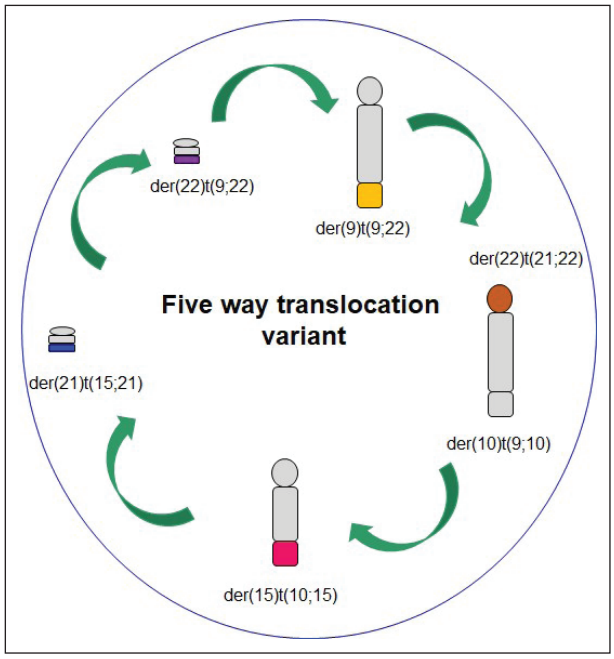

Figure 2. *Diagrammatic representation of Five-way translocation. The representative translocated region on the derivative chromosomes is depicted in different colors.*

In the present study, the patient demonstrated an unusually rapid transformation to blast crisis within 8 months of diagnosis despite early initiation of imatinib therapy. Such rapid progression aligns with previous reports describing aggressive disease biology in patients harboring complex or variant Philadelphia translocations (7,9-11). The limited and transient hematologic response to imatinib, followed by resistance and failure of dasatinib, further suggests that these complex rearrangements may be associated with inherent genomic instability and poor therapeutic response. The eventual fatal outcome within 1 year of diagnosis underscores the need for early identification of high-risk cytogenetic variants and consideration of alternative therapeutic strategies, including early second-generation TKI therapy or hematopoietic stem cell transplantation in suitable candidates.

TKI resistance in such cases may result from co-occurring cytogenetic abnormalities or *BCR*::*ABL1* gene fusion oncogene (12). In our study, the sequencing analysis of the tyrosine kinase domain before the start of imatinib therapy, revealed the presence of e13a2 transcript (p210) which is usually an outcome of alternative splicing mechanisms, a post-transcriptional modification. Studies have suggested the negative impact of imatinib in the patients with complex chromosomal translocation in Ph-positive cases suggesting that clonal evolution could have resulted in genomic instability (13). While no pre-therapy *BCR*::*ABL1* kinase domain mutations were identified, the profound genomic instability suggested by this complex rearrangement may foster other mechanisms of resistance, including the later acquisition of kinase domain mutations or activation of alternative signaling and survival pathways. These possibilities highlight the need for close molecular monitoring in patients with complex cytogenetic variants. Our study adds to the growing understanding of the impact of complex Ph-positive chromosomal abnormalities on the clinical outcomes, and their contribution to TKI resistance, underscoring the need for personalized therapeutic strategies in CML.

Conclusions

This case highlights a novel five-way chromosomal translocation in a patient with Ph-positive CML and rapid disease progression despite first-line TKI therapy. Comprehensive cytogenetic and molecular evaluation is essential for detecting such rare rearrangements, which may predict resistance and unfavorable outcomes. Early recognition of these variants can guide timely therapeutic adjustments and improve disease management.

Acknowledgments

The authors are grateful to the proband and his family members for supporting the case study. The authors would also like to thank the management of Dr. Lal Path Labs for providing excellent diagnostic facilities.

List of Abbreviations

ALL	Acute lymphoblastic leukemia
CML	Chronic myeloid leukemia
FISH	Fluorescence in situ hybridization
Ph-Chromosome	Philadelphia chromosome
TKI	Tyrosine kinase inhibitor

Authorship contribution statement

Investigation, conceptualization, literature survey and manuscript preparation: LR; Chromosomal and FISH analysis: SP, SRM, RK, SJ; Supervision, revision and editing: RK, VKT, VL. All authors read and approved the final manuscript.

Funding

None.

Data availability

The datasets analyzed during the current study are available upon request.

Declarations and Ethics approval

The study was approved by the Ethics Committee of Dr. Lal Pathlabs Ltd. (EC/ NEW/INST/2021/1702).

Consent for publication

Informed and written consent for the publication was obtained from the participants/guardian.

Conflict of interests

The authors declare that they have no competing interests.

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