

Review Article

Adult B-Cell Acute Lymphoblastic Leukemia with Complex Variant Translocation t(9;11;22) (q34;q13;q11) and FISH/Molecular Biology Discordance: A Case Report

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Abstract: Introduction: The Philadelphia chromosome (Ph), resulting from the t(9;22) (q34;q11) translocation, is the most common cytogenetic abnormality in adult acute lymphoblastic leukemia (ALL). Complex variant translocations (vPh) involving a third chromosome are rare, and the involvement of the 11q13 locus (*CCND1*) is exceptional. **Case Presentation:** We report the case of a 67-year-old male presenting with systemic symptoms, splenomegaly, and hyperleukocytosis at 80,000/ μ L. Bone marrow aspirate and immunophenotyping led to a diagnosis of common B-cell ALL (B-ALL II). Cytogenetic analysis revealed a complex translocation t(9;11;22) (q34;q13;q11). Fluorescence *in situ* hybridization (FISH) confirmed a rearrangement involving the *BCR*, *ABL1*, and *CCND1* genes. Unexpectedly, RT-PCR testing for *BCR-ABL1* fusion transcripts (p190, p210, and p230) returned negative results. **Conclusion:** This case illustrates an atypical cytogenetic presentation of B-ALL and underscores the importance of an integrated diagnostic approach. The discordance between FISH and RT-PCR suggests the presence of a cryptic breakpoint or an alternative fusion transcript, highlighting the need for next-generation sequencing (NGS/RNA-Seq) to optimize therapeutic management.

Keywords: B-cell Acute Lymphoblastic Leukemia, Variant Philadelphia Chromosome, Complex Translocation, *CCND1*, FISH-PCR Discordance.

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1. INTRODUCTION

Adult B-cell Acute Lymphoblastic Leukemia (B-ALL) is a hematologic malignancy associated with an unfavorable prognosis. The most frequent recurrent cytogenetic abnormality is the t(9;22)(q34;q11.2) translocation, generating the Philadelphia (Ph) chromosome and the *BCR-ABL1* fusion gene. This abnormality is found in 20% to 30% of adult ALL cases [1].

In rare instances (2% to 9% of Ph+ hematologic malignancies), complex variant translocations (vPh) are observed, involving one or more additional chromosomes alongside chromosomes 9 and 22. While these variants are well documented in Chronic Myeloid Leukemia (CML), they remain exceptional in ALL. Furthermore, the involvement of the *CCND1* gene (located at 11q13) classically associated with mantle cell lymphoma via t(11;14) is an unusual event in ALL pathogenesis [2, 3].

We present an exceptional case of adult B-ALL in a 67-year-old male characterized by a three-chromosome complex translocation t(9;11;22)(q34;q13;q11), accompanied by a major diagnostic discordance between FISH (positive for rearrangement) and conventional molecular biology (negative for *BCR-ABL1* fusion transcripts).

2. Clinical and Biological Case Presentation

A 67-year-old male with no significant past medical history presented to the emergency department with severe fatigue progressing over several days, accompanied by fever and mucocutaneous pallor. Initial physical examination revealed no hemorrhagic signs or peripheral lymphadenopathy; however, abdominal palpation demonstrated splenomegaly.

The complete blood count (CBC) revealed marked hyperleukocytosis at 80,000 leukocytes/ μ L, accompanied by severe anemia (Hemoglobin at 7 g/dL) and thrombocytopenia (Platelets at 51,000/ μ L).

Peripheral blood smear examination showed 70% circulating blast cells.

Bone marrow aspirate examination confirmed massive bone marrow infiltration with 87% blasts. These

cells were small to medium in size, with a high nucleocytoplasmic ratio, fine chromatin, and an absence of distinct azurophilic granules, morphological features strongly suggestive of lymphoblasts. (Figure 1)

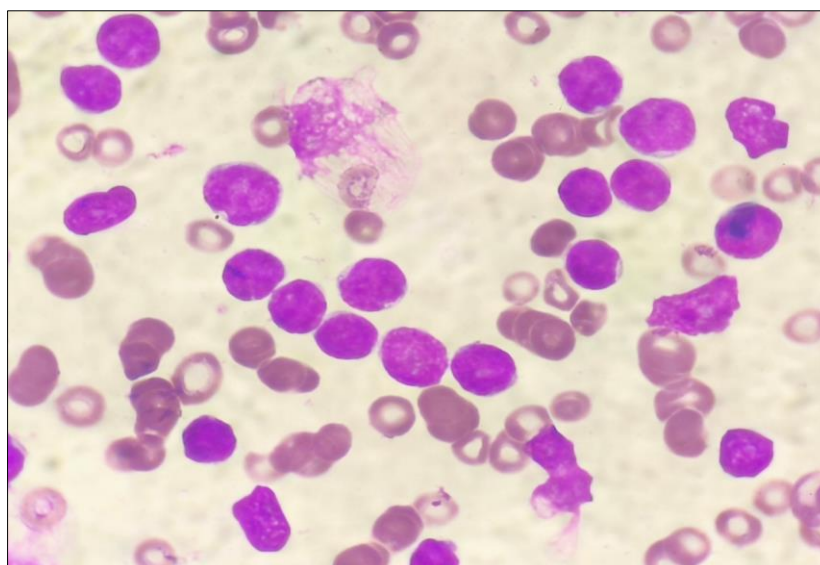


Figure 1: MGG-stained bone marrow smear (x1000): Lymphoblasts

Immunophenotyping on bone marrow blood identified a blast population characterized by dim CD45 expression (CD45 dim) and CD34 negativity. Strong expression of B-lineage markers (CD19+, CD79a+, CD22+) along with CD10 expression established the diagnosis of common B-cell Acute Lymphoblastic Leukemia (B-ALL II).

Cytogenetic analysis (R-banded karyotype) revealed structural chromosomal abnormalities, including a deletion of the short arm of chromosome 7 and a complex translocation involving three chromosomes: 9, 11, and 22. The chromosomal formula was defined as: 46,XY,del(7)(p11),t(9;11;22)(q34;q13;q11). (Figure 2)

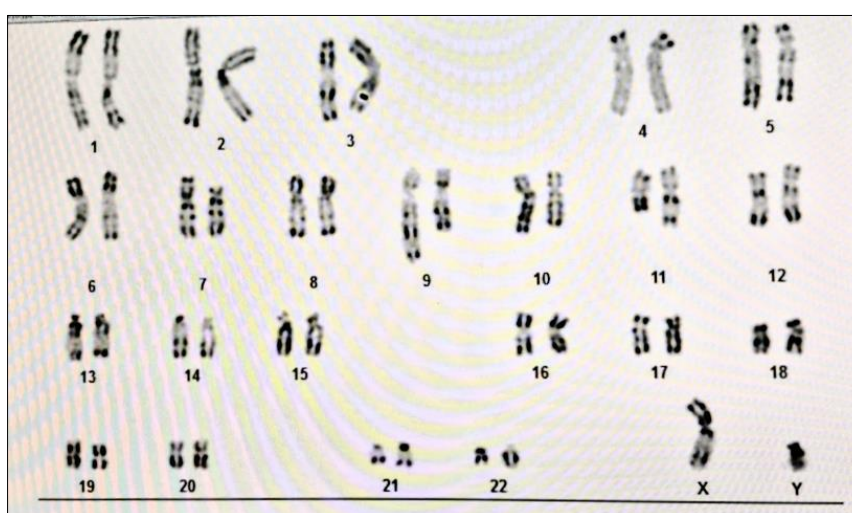


Figure 2: Karyotype (R-banding): 46,XY,del(7)p(11),t(9;11;22)(q34;q13;q11)

To structuralize and characterize this molecular abnormality, fluorescence *in situ* hybridization (FISH) was performed. It confirmed a complex rearrangement involving the loci of the *BCR* (22q11), *ABL1* (9q34), and *CCND1* (11q13) genes.

To confirm the presence of a fusion transcript for targeted therapy, a multiplex RT-PCR was performed on bone marrow RNA. Surprisingly, screening for standard *BCR-ABL1* fusion transcripts (minor m-bcr/p190, major M-bcr/p210, and micro μ -bcr/p230) returned strictly negative.

3. DISCUSSION

This case highlights two major scientific points of interest: the nature of a three-chromosome complex variant translocation involving the *CCND1* locus in B-ALL, and the biological rationale behind a striking discordance between FISH and molecular biology (RT-PCR) testing.

3.1. Variant Translocation t(9;11;22) and *CCND1* Involvement

Variant Philadelphia chromosome translocations result from complex break-and-repair mechanisms. In our observation, the third partner chromosome is chromosome 11 at region q13. This locus houses the *CCND1* gene, which encodes Cyclin D1—a key regulator of the G1/S cell cycle transition.

In the literature, *CCND1* overexpression is the molecular hallmark of mantle cell lymphoma, but it has also been reported as a poor prognostic factor in certain acute leukemias through rearrangements with atypical partner genes. The juxtaposition of *CCND1* within the *BCR/ABL1* complex could lead to aberrant Cyclin D1 overexpression driven by *BCR* promoters, conferring an added proliferative advantage to the blasts. This mechanism could explain the hyperleukocytic presentation (80,000/ μ L) observed in our patient [4].

3.2. FISH and Molecular Biology (RT-PCR) Discordance

The most challenging diagnostic finding is the negative RT-PCR despite a positive FISH result. Although rare, this phenomenon has been described in literature and can be explained by several biological hypotheses:

1. **Cryptic or Atypical Breakpoints:** Standardized RT-PCR primers target canonical breakpoints (exons e1, b2, b3 of *BCR* and a2 of *ABL1*). If the t(9;11;22) translocation generated an unusual exonic or intronic breakpoint, the resulting fusion transcript will not be amplified by standard multiplex PCR panels [5].
2. **Complex Alternative Splicing:** The involvement of chromosome 11 may have created a three-component chimeric gene (*BCR-CCND1-ABL1* or *BCR-ABL1-CCND1*), altering the length or sequence of the transcribed mRNA and rendering it undetectable by conventional PCR probes.
3. **Absence of Functional Transcript:** FISH demonstrates physical proximity of genes at the DNA level. It is possible that this topological

rearrangement does not generate a stable fusion transcript (nonsense-mediated decay), leaving leukemogenesis driven solely by *CCND1* dysregulation or associated loss of heterozygosity.

3.3. Therapeutic Implications

In elderly patients (67 years old), tolerance to intensive chemotherapy is limited. The presence of Ph+ (or "Ph-like") ALL normally indicates the addition of tyrosine kinase inhibitors (TKIs) such as dasatinib or ponatinib. The absence of a standard *BCR-ABL1* transcript precludes measurable residual disease (MRD) monitoring by RT-PCR and calls into question the reliance of blasts on the ABL1 signaling pathway. In such scenarios, whole-transcriptome sequencing (RNA-Seq) or high-throughput next-generation sequencing (NGS) is essential to delineate the exact hybrid transcript structure and confirm the indication for TKI therapy [5].

4. CONCLUSION

We report an exceptional case of adult B-ALL associated with a complex variant translocation t(9;11;22)(q34;q13;q11). This case eloquently illustrates the limitations of targeted molecular biology when confronting atypical chromosomal rearrangements. Whenever a discordance between cytogenetics/FISH and RT-PCR arises, clinicians and cytogeneticists should suspect a variant breakpoint. Molecular characterization via Next-Generation Sequencing (NGS) stands as the gold standard to elucidate the fusion gene architecture, tailor targeted therapy, and establish a personalized marker for minimal residual disease monitoring.

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