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Research Article

A Case of Philadelphia Chromosome-Positive b-Cell Acute Lymphoblastic Leukemia with Trisomy 5 and Monosomy 20: Clinical and Cytogenetic Insights"

Pina J. Trivedi *, Krishna Barad, Nidhi Patel, Rashmi Oza

Cytogenetics Lab, Cancer Biology Department, The Gujarat Cancer & Research Institute, Ahmedabad, Asarwa, Gujarat, India.

***Corresponding Author:** Pina J. Trivedi., Cytogenetics Lab, Cancer Biology Department, The Gujarat Cancer & Research Institute, Ahmedabad, Asarwa, Gujarat, India.

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Abstract

Philadelphia chromosome-positive (Ph+) B-cell acute lymphoblastic leukemia (B-ALL) by the t(9;22)(q34;q11.2) translocation produces the BCR-ABL fusion gene and tends to have an aggressive clinical course. Here, we report a case of a 59-year-old woman with B-ALL carrying a complex karyotype with trisomy 5 (+5) and monosomy 20 (-20) in addition to the classical Ph chromosome. This report summarizes the clinical presentation, hematological and immunophenotypic features, extensive cytogenetic and molecular diagnosis, treatment regimen, and prognostic significance. The coexistence of other chromosomal abnormalities most probably reflects clonal evolution and is associated with a worse prognosis, emphasizing the importance of tailored therapy including tyrosine kinase inhibitors and strict molecular follow-up.

Key words: cell; blood; cancer; hematology

Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy involving uncontrolled growth and infiltration into bone marrow, peripheral blood, and extramedullary sites by immature lymphoid precursors. ALL is the most prevalent pediatric malignancy and constitutes a considerable percentage of adult leukemia, in which it carries a worse prognosis than in pediatric populations [Hunger SP 2015; Robison LL, 2008 et al]. ALL may be broadly categorized according to lineage into B-cell and T-cell subtypes, of which B-ALL is the most common in adults [Terwilliger T et al, 2017]. B-ALL pathogenesis is fueled by heterogeneity of genetic and chromosomal abnormalities that affect the clinical presentation, therapeutic response, and prognosis.

Of these, the most common cytogenetic abnormality found in adult ALL is the Philadelphia chromosome (Ph), resulting from the balanced reciprocal translocation t(9;22)(q34;q11.2) and occurring in about 25-30% of cases [Fielding AK et al, 2008]. The translocation unites the breakpoint cluster region (BCR) gene on chromosome 22 with the Abelson murine leukemia viral oncogene homolog 1 (ABL1) gene on chromosome 9, producing the BCR-ABL fusion oncogene that produces a constitutively active tyrosine kinase [Ottmann OG,et al, 2005]. This BCR-ABL oncoprotein results in abnormal activation of several intracellular signaling pathways, such as RAS/MAPK, PI3K/AKT, and JAK/STAT pathways, which together induce increased cellular proliferation, survival, and drug resistance to apoptosis [Druker BJ,2008 & Ren R, 2005]. The existence of the Philadelphia chromosome classically provides a poor prognosis with elevated rates of relapse and poor long-term survival when managed with standard chemotherapy alone [Cortes JE, et al, 2000]. The advent of tyrosine kinase inhibitors (TKIs), i.e., imatinib, dasatinib, and nilotinib, has changed the treatment paradigm of Ph-positive (Ph+) ALL by specifically inhibiting the BCR-ABL tyrosine kinase activity, leading to elevated remission rates and survival [Kantarjian HM, 2002 & Jabbour E. 2014]. But even with these strides, Ph+ ALL continues to be a problematic clinical entity, especially in elderly patients, owing to high rates of resistance mechanisms, clonal evolution, and the presence of other cytogenetic abnormalities affecting disease severity and treatment outcome [Moorman AV, et al, 2013]. Cytogenetic and molecular diversity aside from the signature t(9;22) translocation has been noted as a poor prognostic factor in Ph+ ALL. Other abnormalities are noted in most patients at presentation and tend to reflect secondary clonal events incurred over the course of the disease or secondary to genomic instability caused by the BCR-ABL Oncoprotein [Enshaei A,

2016 & Shukla N, 2015]. These secondary abnormalities can consist of numerical and structural changes, e.g., trisomy, monosomy, deletions, and complex karyotypes, that can influence leukemic biology and affect therapeutic responses [Grimwade D. et al 2015]. Among the less commonly reported but clinically significant secondary abnormalities in Ph+ ALL are trisomy 5 (+5) and monosomy 20 (-20). Trisomy 5 is the addition of an extra copy of chromosome 5 that contains genes related to cell cycle regulation, DNA repair, and signal transduction that could provide elevated proliferative ability and survival of leukemic blasts [Schwab C, 2013 & Tobal K, 2001]. Monosomy 20, or uniparental loss of a copy of chromosome 20, could result in haploinsufficiency of tumor suppressor genes and interruption of normal hematopoietic control, hence promoting leukemic development and drug resistance [Huret JL., 1985 & Schwab C,2003]. Herein, we present a 59-year-old female who was diagnosed with Ph+ B-ALL with a complex karyotype of trisomy 5 and monosomy 20 in combination with the characteristic t(9;22)(q34;q11.2) translocation. We present a comprehensive clinical, hematological, immunophenotypic, cytogenetic, and molecular study, and we discuss how these combined abnormalities affect disease evolution and treatment. By this case, we seek to highlight the value of meticulous cytogenetic analysis in adult ALL and review the existing knowledge on secondary chromosomal aberrations in shaping prognosis and therapy in Ph+ ALL.

Case Details

A 59-year-old female patient presented with clinical suspicion of acute leukemia. Initial radiological evaluations, including chest X-rays and ultrasound abdomen, were largely unremarkable except for fatty infiltration of the liver. MRI and CT imaging showed no intracranial abnormalities but revealed degenerative changes in vertebrae and pulmonary findings consistent with possible infective/inflammatory pathology.

Laboratory Investigations:

Hematology: Bone marrow aspiration showed hyper cellularity with 89% blasts (medium-sized cells with high nuclear-to-cytoplasmic ratio and irregular nuclei), suppressed erythropoiesis, and absence of megakaryocytes. Peripheral blood smear revealed normocytic hypochromic anaemia, moderate leucocytosis with 95% blasts, and severe thrombocytopenia.

Histopathology: Bone biopsy showed replacement of normal hematopoietic elements by sheets of blasts, consistent with acute leukemia. Immunophenotyping (Flow Cytometry): Blasts expressed B-cell markers (CD19, CD10, CD79a) and stem cell marker CD34, along with aberrant expression of myeloid markers CD13 and CD33. The immunophenotype was consistent with precursor B-cell ALL.

Molecular Diagnostics: RT-qPCR detected BCR-ABL transcripts, with a notable presence of minor BCR-ABL fusion gene copies, confirming Ph-positive ALL.

Diagnosis: B-Cell Acute Lymphoblastic Leukemia (B-ALL) with Philadelphia chromosome positivity (BCR-ABL fusion gene).

Treatment and Clinical Course: The patient received induction and consolidation chemotherapy including drugs such as Rasburicase, Vincristine, Methotrexate, Daunorubicin, and Dasatinib (a tyrosine kinase inhibitor targeting BCR-ABL). Serial bone marrow examinations after therapy indicated hematological recovery with controlled leukemic activity and no increase in blasts. The institutional review board approved the present study, and the patient's informed consent was obtained.

Materials and Method:

Conventional Cytogenetics

A sample of bone marrow was aseptically aspirated in a Sodium Heparinized vacutainer. A short-term culture was performed according to standard protocols for routine cytogenetic investigation. The slides were stained with the Giemsa Trypsin G-banding technique. High-grade metaphases were photographed with the aid of a Zeiss automated karyotyping system and analyzed using IKAROS software. The karyotype was described in accordance with ISCN 2020 guidelines.

Fluorescence in situ hybridization (FISH)

Using an Epi-fluorescence microscope (AXIO Imager.Z2, Zeiss, USA) fitted with the proper filter sets, photographs were taken and examined using the ISIS FISH imaging system (Metasystems, Germany). The FISH probe BCR_ABL was labeled with: Orange signal for the ABL gene on chromosome 9q34 & Green signal for the BCR gene on chromosome 22q11.2. The FISH probe is labelled with: Orange signal for the 5q31 both loci Green signal for the centromere of chromosome 5.

Results:

Conventional Cytogenetic:

Traditional chromosome analysis during diagnosis of GTG-banded metaphases was performed. 20 metaphases were karyotyped. The sample reveals 46 chromosomes with trisomy 5 and monosomy 20 and translocation 9 and 22 in every metaphase. All metaphases revealed 46,XX,+5,-20,t(9;22)(q34;q11.2)[20] detailed in figure.

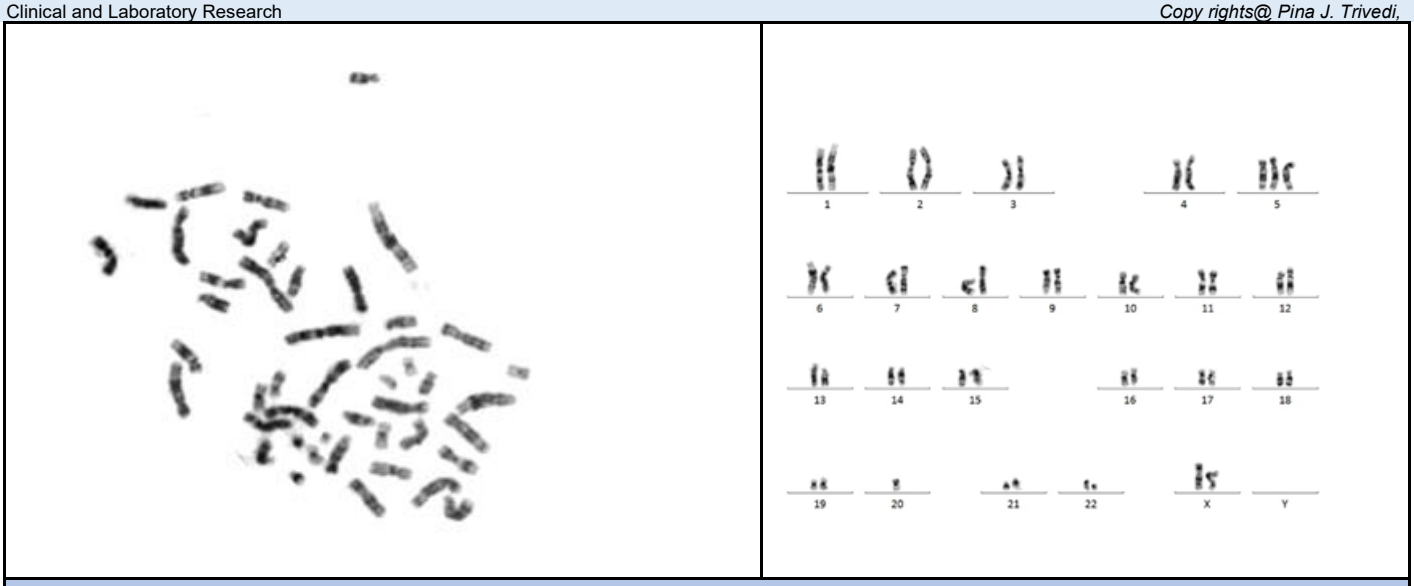

Figure 1: Representative images of Conventional cytogenetic results of GTG banded karyotype showing 46,XX,+5,-20,t(9;22)(q34;q11.2)

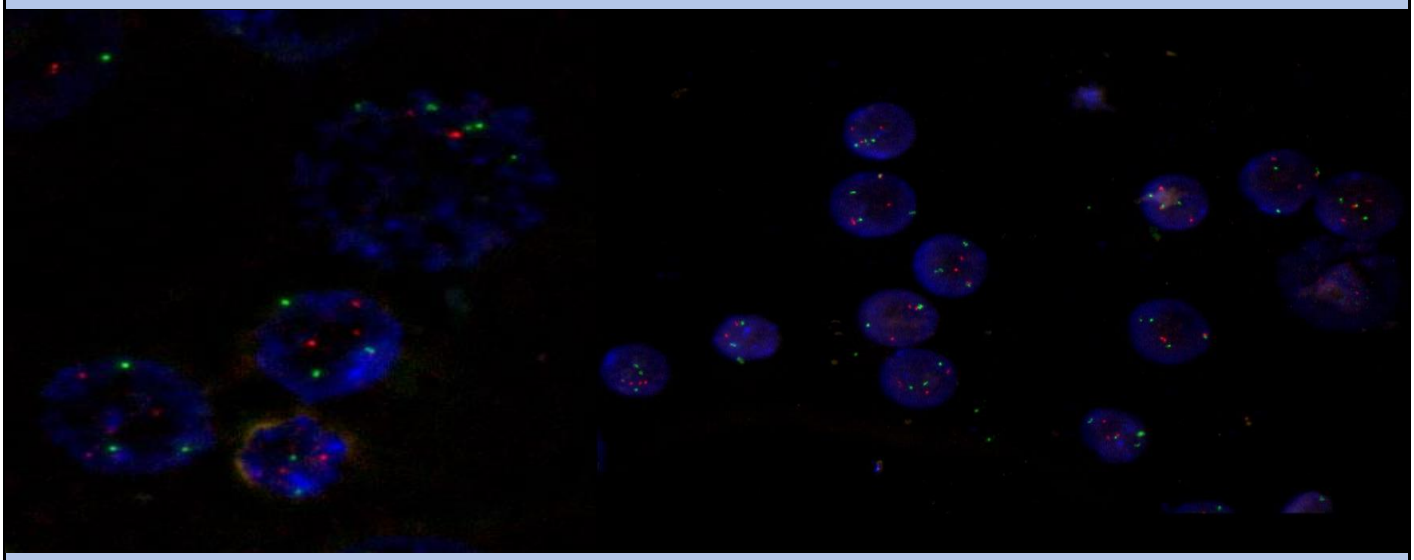

Figure 2: Representative image of FISH showing 3 green signals indicates trisomy of chromosome 5. Observed 3O3G signals in Interphase but may be due to **mosaic population** of cells we did not get the possible signals in Metaphase.

Fish:

BCR-ABL DC DF probe results expressed metaphases with 1O1G2F signals. Sample exhibited fusion for the BCR.ABL gene. FISH result indicates that the sample has gene fusion. FISH report was nuc ish(ABL1,BCR)x3(ABL1 con BCRx2)[200]. FISH analysis was performed on a short-term cultured bone marrow sample using dual-color probes targeting the 5q31 region (orange signal) and the centromere of chromosome 5 (green signal). All 200 interphase nuclei examined showed 3O3G signal pattern, indicating an extra copy of both the 5q31 locus and the centromere region. The result, reported as nuc ish(EGR1, D5S23, D5S721)x3[200], confirms the trisomy of chromosome 5 in this patient.

Discussion

The Philadelphia chromosome (Ph), the product of the reciprocal translocation t(9;22) (q34;q11.2), is a characteristic genetic abnormality of adult ALL and CML [Ren R, 2005 & Wassmann B, 2005]. The translocation produces the BCR-ABL fusion gene, coding for a constitutively active tyrosine kinase that aberrantly regulates multiple downstream signalling cascades, including RAS/MAPK, PI3K/AKT, and JAK/STAT, to sustain leukemic cell growth and survival [Deininger MW,2000 & Pui CH 2006].

Ph+ ALL represents about 25-30% of adult ALL and is more frequently seen in older adults [Fielding AK, et al 2008]. In the past, Ph+ ALL was linked to a dismal prognosis because of the disease's aggressive nature and chemotherapy resistance, and long-term survival rate was less than 20% [Kantarjian, 2002 & Jabbour E.,2014]. The advent of tyrosine kinase inhibitors (TKIs) such as imatinib and subsequent-generation agents like Dasatinib and Ponatinib dramatically altered the treatment paradigm, raising remission rates and overall survival [Cortes JE, et al 2012]. Even with these developments, resistance to TKIs is often encountered because of kinase domain mutations, subclonal heterogeneity, and other genetic mutations, highlighting the complexity of Ph+ ALL and the necessity for thorough genetic assessment [Harrison CJ. Et al, 2013]. Secondary cytogenetic aberrations present with the Ph chromosome are not infrequent and occur in about 60-70% of adult Ph+ ALL patients at diagnosis [Moorman AV, et al, 2012].

These are the abnormalities that are assumed to arise from genomic instability induced by BCR-ABL kinase activity, clonal evolution under selective pressure, or intrinsic defects in DNA repair mechanisms [Schwab C et al, 2013]. Secondary abnormalities include numerical aberrations such as trisomies and monosomies, deletions, and complex rearrangements. Their presence in general characterizes a complex karyotype, which is an independent poor prognostic factor in Ph+ ALL and other hematologic malignancies[Grimwade D, et al 1998 .& Harrison CJ, 2003].Trisomy 5 (+5) and monosomy 20 (-20) were detected in addition to the typical t(9;22)(q34;q11.2) translocation in this instance, indicating such complex karyotypic evolution[Huret JL et al, 1985].

Trisomy 5 is fairly rare but important in acute leukemias. The advantage of an additional chromosome 5 can result in overexpression of oncogenes or regulatory genes on 5q, such as genes controlling the cell cycle (e.g., CDC25C), apoptosis, and DNA repair [Moorman AV, et al., 2010]. Trisomy 5 usually occurs with clonal evolution and progression in AML and ALL. Studies have linked +5 to adverse clinical features such as high leukocyte count, resistance to chemotherapy, and shorter survival times [Fielding AK et al, 2007]. In the context of Ph+ ALL, trisomy 5 may contribute to leukemic cell proliferation and therapeutic resistance, although specific prognostic data remain limited [Jabbour E, et al, 2012]. Monosomy 20 or loss of the long arm of chromosome 20 (20q) is a highly reported abnormality in myeloid neoplasms and less commonly in lymphoid leukemia [Topp MS, et al, 2015]. Chromosome 20 contains significant tumor suppressor genes, including L3MBTL1 and SGK2, which play a role in cell proliferation and regulation of apoptosis [Maude SL, et al, 2014]. Missing one copy of chromosome 20 may lead to haploinsufficiency of these genes, which will favor leukemogenesis by allowing unrestricted cell growth and loss of apoptotic response. Monosomy 20 has been reported in acute leukemias as a marker of a poor prognosis and higher relapse risk. Although monosomy 20 is less frequently documented in Ph+ ALL, when present in a compound karyotype, it can further increase disease aggressiveness and resistance to treatment [Enshaei A. et al, 2016]. Complex karyotypes—three or more chromosomal abnormalities—are becoming more widely accepted as significant prognostic indicators in hematologic malignancies. In Ph+ ALL, patients with complicated karyotypes frequently have lower response rates, more frequent relapses, and lower overall survival than patients with sole Ph chromosome [Ren R, 2005 & Wassmann B, 2005]. The presence of trisomy 5 and monosomy 20 together in this patient is an example of clonal evolution that most probably indicates selection of leukemic subclones with survival and resistance advantage. Such complexity requires intensified treatment strategies [Jabbour E, et al, 2012]. Management of Ph+ ALL patients with complicated karyotypes is still difficult. Early and active TKIs (Dasatinib, Ponatinib) can overcome partial resistance but are not adequate on their own in most instances. HSCT is the sole potentially curative therapy and must be considered early, particularly for complicated karyotype patients [Fielding AK, et al 2008].

Conclusion:

This case points to the clinical complexity and prognostic implication of Ph+ B-ALL in the presence of unusual cytogenetic changes like trisomy 5 and monosomy 20. Although the presence of the BCR-ABL1 fusion gene still is the main driver of disease and treatment choice, other chromosomal aberrations can influence disease course, treatment response, and final prognosis. Extensive cytogenetic analysis is necessary in such situations to clarify the biological behavior of the disease and to individualize treatment protocols. Additional studies and collection of further similar cases are indicated to define the clinical significance of these rare cytogenetic combinations.

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