




# B-Lymphoblastic Leukemia Presenting with an Iso derivative Philadelphia Chromosome—A Rare Case Report and Review of Literature

Neelum Mansoor<sup>1</sup>  Sidra Maqsood<sup>2</sup> Syeda Ambareen Zehra<sup>1</sup> Imad Bakri<sup>3</sup>

<sup>1</sup> Department of Hematology & Blood Center, Indus Hospital & Health Network, Karachi, Pakistan

<sup>2</sup> Offices of Research, Innovation and Commercialization, Indus Hospital & Health Network, Karachi, Pakistan

<sup>3</sup> Zilgene Clinical Lab Consulting, Atoko Way, San Antonio, Texas, United States

**Address for correspondence** Neelum Mansoor, FCPS, Consultant Hematologist, Indus Hospital & Health Network, Korangi Campus, Plot C-76, Sector 31/5, Opposite Darussalam Society Korangi Crossing, Karachi -75190, Pakistan (e-mail: neelum.mansoor@tih.org.pk).

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## Abstract

The Philadelphia chromosome is seen in 5% of pediatric and 25 to 50% of adult cases of acute lymphoblastic leukemia (ALL). It is linked to aggressive illness with a dismal prognosis. Additional chromosomal abnormalities are not prevalent with translocation 9;22; nevertheless, isochromosome derivative [ider(22)] with this translocation is rarely recorded in the literature. This is the third instance of ider(22) in pediatric B-cell acute lymphoblastic leukemia (B-ALL). Bone marrow chromosome analysis by G-banding showed 46,XX,t(9;22)(q34;q11.2)[6]/46,XX,ider(22)(q10)t(9;22)(q34;q11.2)[14]. Fluorescence in situ hybridization (FISH) analysis for *BCR::ABL1* fusion showed 40% of interphase cells with two and 35% with three fusion signals that were in concordance with the karyotype. The patient was categorized as National Cancer Institute (NCI) high-risk (HR) and started with HR chemotherapy according to Children's Oncology Group (COG) protocol. Postinduction remission assessment by flow cytometry showed 2.6% measurable residual disease. The case highlights significance of cytogenetic analysis despite availability of advanced techniques like FISH. The prognostic significance of concurrent ider22(q10) with t(9;22) is yet to be explored.

## Keywords

- ▶ acute lymphoblastic leukemia
- ▶ immunophenotyping
- ▶ Philadelphia chromosome
- ▶ cytogenetic analysis
- ▶ measurable residual disease

## Introduction

Philadelphia (Ph) chromosome is less often found in B-cell acute lymphoblastic leukemia (B-ALL) patients; however, it is commonly (90–95%) present in chronic myeloid leukemia (CML) patients.<sup>1,2</sup> Ph chromosome can be detected in about 25% of adult ALL and only 2 to 4% of pediatric ALL.<sup>1,3</sup> Presence of double Ph chromosome is infrequent in ALL but reported in some cases of CML during the blast crisis phase.<sup>4</sup> When compared to Ph chromosome-negative ALL, Ph chromosome-positive ALL is typically associated with a more aggressive disease that may be more resistant to treatment and can have a poorer prognosis compared to other types of pediatric

ALL.<sup>1,5</sup> Currently, the mainstay of treatment is a tyrosine kinase inhibitor plus intensive chemotherapy, followed by hematopoietic stem cell transplant (HSCT) after the first remission.<sup>6</sup> We report a rare case of a 4-year-old girl diagnosed as a case of isoderivative Ph chromosome-positive B-ALL. This chromosomal aberration is exceptionally rare in B-ALL. The case is being reported to spread awareness about significant additional cytogenetic findings in a case of B-ALL with recurrent cytogenetic abnormalities. This patient also revealed other poor clinical features like hyperleukocytosis at the time of presentation and did not achieve postinduction remission.

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### Case Report

A 4-year-old girl presented to emergency department of pediatric oncology unit with a history of recurrent epistaxis for 2 months and was severely anemic. There is no significant history of any past illness and/or genetic disease in the family. On general physical examination, she had lymphadenopathy and hepatosplenomegaly.

### Differential Diagnosis, Investigations, and Treatment

Complete blood count showed hyperleukocytosis with white cell count of  $153 \times 10^9/L$ , anemia with hemoglobin of 7.5 gm/dL, and thrombocytopenia with a platelet count of  $18 \times 10^9/L$ . Blood film showed a leucoerythroblastic picture with 84% blasts. Immunophenotyping performed on peripheral blood using 8-color flow cytometry (BD FACS Canto II) revealed the following immunophenotypic profile:

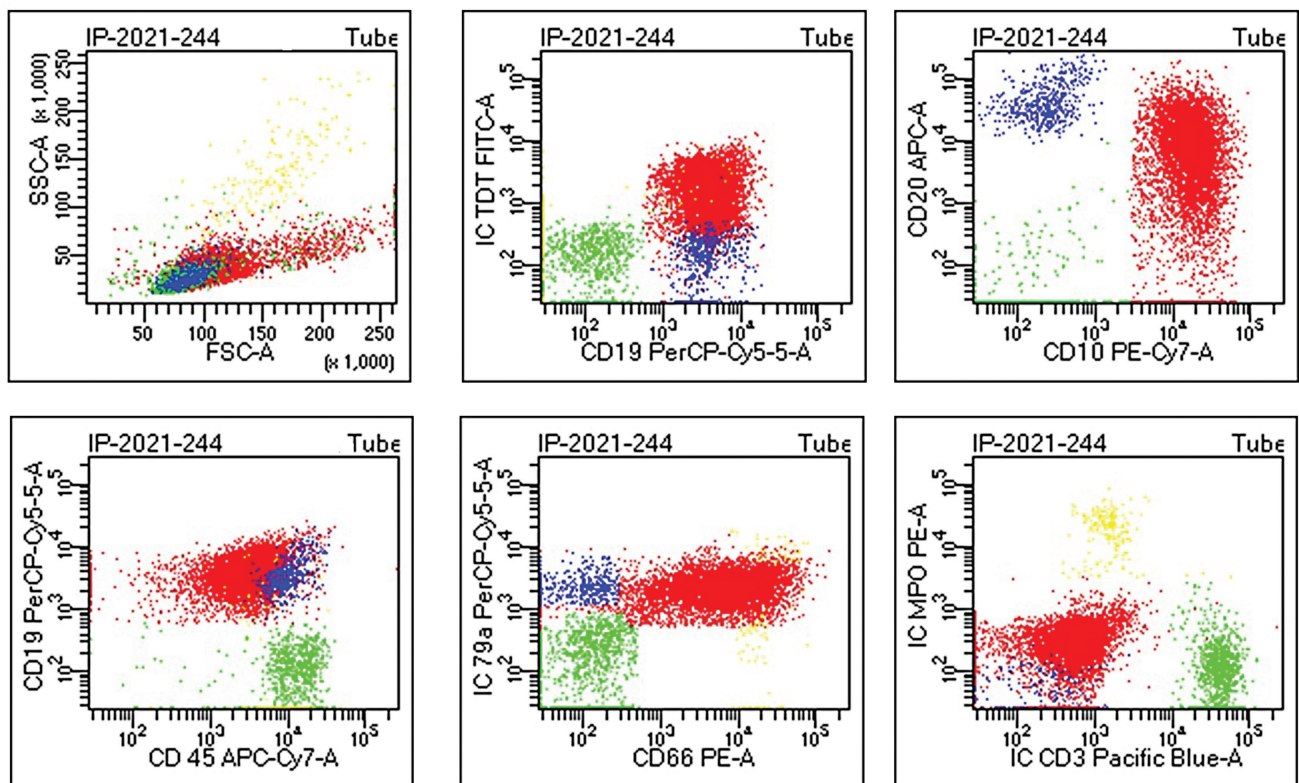
- Positive for CD34, CD45, CD19, CD79a, CD20, CD10, CD66, CD9 and CD58
- Negative for intra-cytoplasmic CD3, intra-cytoplasmic MPO, CD13, CD33

On the basis of flowcytometry, the case was diagnosed as B-ALL (►Fig. 1). Other laboratory investigations including liver and kidney function tests were within normal range; however, serum albumin was low (2.0 g/dL). The diagnostic lumbar puncture for central nervous system (CNS) infiltra-

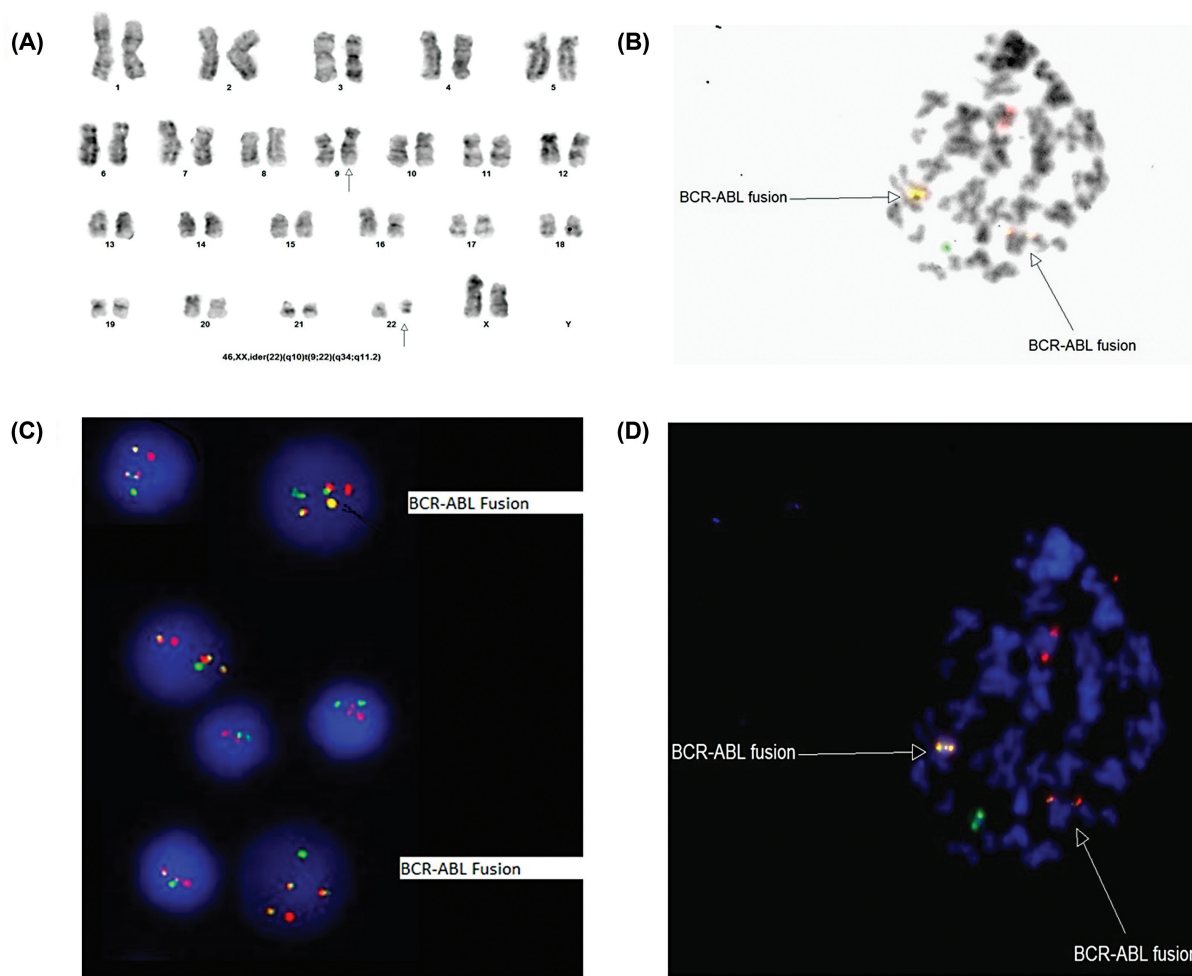
tion showed CNS1 status that is consistent with absence of blasts. Bone marrow specimen was received for fluorescence in situ hybridization (FISH) and cytogenetic analysis by G-banding (►Fig. 2). Interphase FISH revealed atypical signal pattern, comprised of three fusion signals that were further evaluated by metaphase FISH (►Fig. 2B–D). FISH analysis of the bone marrow for *BCR::ABL1* dual color dual fusion probe using Leica Biosystems automated cell imaging system (CytoVision) detected 70% of *BCR::ABL1* fusion with 35% of those cells harboring three fusion signals, indicating the presence of extra Ph chromosome. Karyotype analysis revealed the presence of an abnormal female chromosome complement comprised of two related cell lines. The first cell line (stem line) was seen in six cells with a Ph chromosome derived by a balanced translocation between the long arms of chromosomes 9 and 22. The second cell line (side line) is seen in 14 cells with an isochromosome for the long arm of chromosome 22 resulting by  $t(9;22)$  (►Fig. 2A) These findings were consistent with FISH results. Translocation (9;22) results in the fusion of the *ABL1* gene at 9q34 and the *BCR* gene at 22q11.2 that is associated with poor prognosis in B-ALL. The presence of *ider(22)* is very uncommon in pediatric B-ALL. She was categorized as NCI high-risk and received modified COG protocol along with Tyrosine kinase inhibitor (TKI).

### Outcome and Follow-Up

Postinduction bone marrow aspirate on morphological review showed remission; however, measurable residual



**Fig. 1** Flow cytometry showing positivity for Tdt, CD19, CD10, CD20, CD45, CD79a, CD66 (color code: red = blasts, blue = B-lymphocytes, green = T-lymphocytes, yellow = granulocytes).



**Fig. 2** (A) Karyotype, (B) met FISH with inverted 4'6-Diamidino-2-phenylindole (DAPI), and (C) interphase fluorescence in situ hybridization (FISH), (D) met FISH.

disease assessment by flowcytometry showed 2.6% residual disease. A HSCT was not possible due to financial constraints; therefore, chemotherapy was adjusted accordingly. Currently, she is on high-risk consolidation chemotherapy.

We have summarized the features of our study case and other published cases in ► **Table 1**.

## Discussion

Despite recent advancement in molecular techniques, several multicenter studies still emphasize significance of cytogenetic studies in determining prognosis of numerical and structural aberrations in hematological neoplasms. Chromosome analysis at the G-band level is still the most important investigation in B-ALL.<sup>7</sup> FISH techniques are used to identify specific structural aberrations that played a vital role in risk stratification of B-ALL and have been implicated in all treatment protocols.<sup>8</sup> But FISH has its own limitations due to targeted technique that does not help in identifying whole genetic makeup of an individual.

Acute leukemia with *BCR::ABL1* is currently classified as high-risk subgroup that requires intensive chemotherapy to achieve optimum response in terms of hematological remission. Few cases were reported with isochromosome 9 with

Ph<sup>+</sup> in pediatric ALL patients.<sup>9–12</sup> However, the isochromosome of the long arm of derivative chromosome 22 from t(9;22) with a deletion of 22p, *ider(22)(q10)t(9;22)* is very rare. To the best of our knowledge, this is the third case of *ider(22)* in B-ALL; the first case was reported by Yamamoto et al and the second case was of an adult woman with *ider(22)* with Ph<sup>+</sup> B-ALL was reported by Meza-Espinoza et al.<sup>13,14</sup>

Yamamoto et al<sup>13</sup> reported the first case of *ider(22)* chromosome in acute leukemia similar to this case. U-type sister chromatid exchange is the probable hypothesis behind *ider(22)* chromosome formation. The *ider(22)* chromosome is pathologically considered equivalent to the presence of double Ph chromosome, which is the most frequent additional aberration in such cases, known to be one of the main secondary chromosomal changes related to the clonal evolution of cells with t(9;22).<sup>15</sup>

Concomitantly with clonal divergence, this patient was presented with hyperleukocytosis that is also an established poor prognostic factor. CNS infiltration was not observed in this case but despite intensive chemotherapy along with timely administration of TKI, she could not achieve post-induction remission. Reported cases with *ider(22)* showed frequent involvement of CNS by leukemic cells at the time of diagnosis.<sup>14</sup>

**Table 1** Features of our case study and published cases with *ider(22)*

Studies	Age/ Sex	Clinical features	G-banding or FISH Analysis	Treatment	Outcome
Ramachandran et al (2016) <sup>16</sup> <i>Patient 1</i>	29y/M	Massive splenomegaly	46,XY,der(9)t(9;22)(q34.13;q11.23), ider(22) (p12)t(9;22)[7]/47,sl, + ider(22)[21]/48,sl; + ider(22)[2]	IM 400 mg daily (8.5 years)	BM study revealed 8% blasts, suggestive of CML-CP. The patient was started on second line TKI, dasatinib, and attained hematological remission 1 month later; now he is on dasatinib for 2 months
<i>Patient 2</i>	51y/M	Moderate splenomegaly	46,XY,t(9;22)(q34.13;q11.23)[4]/ 46,-der(22)t(9;22), +ider(22)(p12)t(9;22)[4]/47,sl1, + ider(22)[13]/48,sl, +der(22), + ider(22)[4]/47,sl, + 8[5]	IM 400 mg daily (6 months)	Initially responded, but subsequently lost the hematologic response. Switch to second line TKI, dasatinib
Meza-Espinoza et al (2016)	54y/F	-	46,XX,t(9;22) (q34;q11.2)[3]/46, idem,ider(22)(22pter→ 22q11.2::9q34→9q? tel::9q?tel→ 9q34::22q11.2→22pter)[14]/46, idem,t(13;17) (q14;q25)[3]/46, idem, + 1,dic(1;1)(?;?), t(13;17)(q14;q25) [8]/46,XX[1]	Received vincristine, prednisone, and daunorubicin-based chemotherapy	04 months later, the patient died after infiltrations were detected both to the retro-ocular and central nervous systems
Our study	4y/F	Lymphadenopathy and hepatosplenomegaly	46,XX,ider(22)(q10)t(9;22)(q34;q11.2)	She was categorized as NCI high-risk and received modified COG protocol along with imatinib	Postinduction bone marrow aspirate on morphological review showed remission however measurable residual disease (MRD) assessment by flowcytometry showed 2.6% residual disease

Abbreviations: BM, bone marrow; CML, chronic myeloid leukemia; CP, chronic phase; FISH, fluorescence in situ hybridization; IM, imatinib; TKI, tyrosine kinase inhibitor.

These cases are evidence of clonal evolution in B-ALL and warrant complete cytogenetic studies in all patients to determine any high-risk factor. According to published literature, relapse is common in cases with additional cytogenetic aberrations in B-ALL.<sup>13</sup>

Availability of complete diagnostic profile and timely workup of this case played a significant role in the management of this patient. The findings were further verified by metaphase FISH in parallel. Tyrosine kinase inhibitor inhibitor was timely added to her B-ALL protocol. However, HSCT could not be offered as the said facility is not currently available in our unit and they could not get it done privately due to financial constrain. Owing to the dismal outcome of chemotherapy in these patients, HSCT is the treatment of choice. Polymerase chain reaction is the recommended modality to monitor molecular response in these patients that should be incorporated in such cases. Monitoring for genetic evolution and molecular response are the future perspectives to impact the outcome of these patients.

## Conclusion

We highlight the significance of cytogenetic aberrations in pediatric B-ALL patients. Further studies are needed to provide insight into this rare subgroup and understand the disease course of these patients with newer therapeutic protocols.

### Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

### Authors' Contributions

Neelum Mansoor is involved in the study of concept and design. Syeda Ambareen Zehra did the acquisition of data. Sidra Maqsood drafted the manuscript. Imad Bakri was involved in the critical revision of the manuscript for important intellectual content. Sidra Maqsood and Syeda Ambareen Zehra are involved in administrative, technical, and material support. Neelum Mansoor supervised the study.

### Authors' Statement

The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

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### Conflict of Interest

The authors declare that they have no conflict of interest.

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