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CASE REPORT

Acquired duplication of isochromosome 21 resulting in pentasomy 21 with concurrent 13q deletion in acute lymphoblastic leukemia: a rare co-occurrence; review of literature.

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ABSTRACT

Background: Pentasomy involving duplication of isochromosome *21;der(21;21)(q10;q10)* is a rare cytogenetic abnormality linked primarily to acute lymphoblastic leukemia (ALL) and less frequently to acute myeloid leukemia (AML) or myelodysplastic syndrome. This abnormality often occur in complex karyotypes and might co-occur with *t(12;21).*

Case Presentation: A unique case of ALL was reported in a 14-year-old male presented with pentasomy 21 from duplicated *der(21;21)(q10;q10)* along with deletion 13q as primary abnormalities. Bone marrow and flow cytometry showed 90% B-lymphoid blast cells. Chromosome analysis and Fluorescence *in situ* hybridization revealed interstitial deletion 13q and *der(21;21)(q10;q10)* duplication; resulting in five *RUNX1* gene signals. While duplicated isochromosome/isodicentric chromosome 21 was documented in isolated cases of ALL and AML, this was the first report of this abnormality co-existing with deletion 13q in the present case of ALL, suggesting a unique contribution to disease pathogenesis. The amplification of 21q genes, including *RUNX1, ETS, and ERG,* might influence pathogenesis and warrants further investigation.

Conclusion: The co-occurrence of Pentasomy 21 and 13q deletion represented a first report, prompting investigations into their combined impact on clinical outcomes. This unique cytogenetic combination highlighted the need for further studies to understand its impact on ALL pathophysiology.

Keywords: Derivative (21;21)(q10;q10), fluorescence *in situ* hybridization, karyotype, pentasomy 21, acute lymphoblastic leukemia.

Introduction

Chromosomal alterations as structural and numerical changes in chromosome 21 and chromosome 13, are commonly observed in hematological malignancies.

Among the different structural and numerical abnormality patterns of chromosome 21 amplification in the form of isochromosome *21/der(21;21)(q10;q10)/Isodicentric chromosome 21* is a rare abnormality seen in acute lymphoblastic leukemia (ALL), typically associated with complex karyotypes. In some instances, *der(21;21)(q10;q10)* has shown co-occurrence with a recurrent translocation of *t(12;21)* in pediatric ALL, and it was also observed in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [1,2].

A study by Mitchell et al. [3] identified isochromosomes in the form of *der(21;21)(q10;q10)* as a significant chromosomal abnormality in hematologic malignancies, linking its presence to various forms of leukemia in disease progression.

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The rare occurrence of duplicated isochromosome 21s in pediatric ALL and its potential clinical impact was emphasized for its role in a better prognosis in comparison to other isochromosomes with a gene dosage effect with overexpression of specific genes that contributed to the proliferation of leukemic cells [4,5].

On the other hand, deletion 13q another distinct rare entity in childhood ALL was reported to be associated with poor prognosis particularly due to the loss of tumor suppressor genes present near the *D13S319* region which has been documented as a critical event in disease progression [6].

Most commonly *der(21;21)(q10;q10)* and the 13q deletion are typically associated with complex karyotypes involving secondary events. The Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer reports approximately 48 cases of derivative chromosomes in the form of *isodicentric (21) (IDIC),* with variations in breakpoints, including around 26 cases involving centromeric breakpoints region p11. Duplication of *IDIC(21)* was observed in 7 cases, with only 2 instances reported as primary sole abnormalities. The co-occurrence of duplication of *derivative (21;21)* and 13q deletion as distinct sole primary cytogenetic abnormalities contributing to dosage effect variations in ALL is extremely rare [7].

This case study represented the 5th reported instance of a primary sole duplicated *der(21;21)(q10;q10)* abnormality and the first to involve the co-occurrence of 13q deletion as a primary event, suggesting their joint role in the pathogenesis of the disease.

Case Presentation

The present case was of a 14-year old boy who presented with a one-month history of fatigue, intermittent fever, night sweats, weight loss, poor appetite, nausea, and knee pain, along with multiple enlarged cervical lymph nodes (more prominent on the right side), ranging from 2 to 4 cm, non-tender, hard, and immobile were observed. There were no palpable axillary or inguinal lymph nodes. The patient had no significant family history of malignancies, including lymphoma or leukemia.

Laboratory results showed normal sodium, potassium, serum creatinine, and liver function tests, but elevated lactate dehydrogenase (291U/l) and uric acid levels (506 µmol/l).

A peripheral blood smear revealed 61% blasts, with a complete blood count showing an elevated white blood cell count (65.95 × 10^3/µl), low hemoglobin (9.5g/dl), and a low platelet count (62 × 10^3/µl). The peripheral blood smear showed leukocytosis with 61% circulating blasts with a high N/C ratio and distinct nucleoli (Figure 1).

A chest X-ray was unremarkable, and CT scans of the chest, abdomen, neck, and pelvis were performed. Bone marrow (BM) aspiration analysis at diagnosis showed hypercellular bone marrow with approximately 95% blast infiltration, marked depression of trilineage hematopoiesis. The blast exhibited a high N/C ratio and distinct nucleoli, some showed cytoplasmic blebs and/or pseudopods (Figure 2).

Immunostaining showed diffuse positive CD34 (D), CD79a (E), and CD10 (F), denoting B-Lymphoblasts. BM aspirate smear showed hypercellular bone marrow

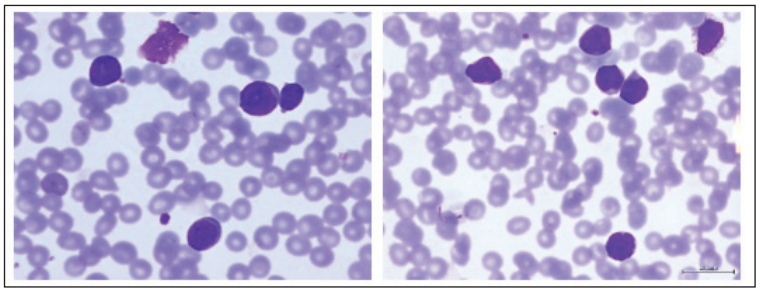

Figure 1. *Peripheral blood smear showing blast cells with a high N/C ratio and distinct nucleoli.*

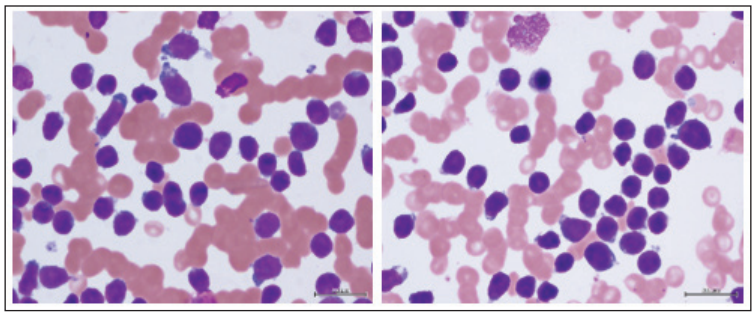

Figure 2. *Bone marrow aspirate smear showing hypercellular bone marrow and total infiltration with blast cells having a high N/C ratio and distinct nucleoli, some show cytoplasmic blebs and/or pseudopods.*

and total infiltration with blast cells having a high N/C ratio (Figure 3).

Flow cytometry of peripheral blood identified 88% blasts which were positive for CD34, TdT, CD19, CD79a, CD10, CD81, CD86 and negative for CD20, CD13, CD11b, CD14, CD15, CD16, CD64, CD117, CD56, CD3, CD2, CD5, CD4, and CD8 and partially positive for HLA-DR, CD33, CD7, CD58 (Figure 4).

These findings were consistent with a diagnosis of B-acute lymphoblastic leukemia, specifically common Pre-B ALL. At diagnosis RT-PCR for BCR/ABL1 fusion, a common genetic marker, was negative, and cerebrospinal fluid analysis showed no involvement.

The patient commenced treatment on the BFM Induction IA protocol for ALL. After completing the BFM Induction IA Protocol, the patient underwent repeat bone marrow aspiration and flow cytometry that revealed a complete remission (CR) with minimal residual disease (MRD) of 0.02%. Throughout the treatment protocol, the patient continued to maintain MRD-negative with no signs of CNS involvement or other complications noted during his treatment course.

Two fully HLA-matched donors were identified for potential allogeneic stem cell transplantation, which is being considered if CR is not achieved. Chromosome analysis and Fluorescence *in situ* hybridization (FISH) analysis showed two abnormalities deletion 13q and *der(21;21)(q10;q10)* with duplication in all the metaphase cells analyzed represented as 47,XY,del(13)(q12q14),der(21;21)(q10;q10)x2[20] (Figure 5).

Fluorescence *in situ* hybridization demonstrated two *RUNX1* signals on each of the *der(21;21)(q10;q10),* resulting in a total of five *RUNX1* signals and interstitial deletion 13q in 95% of interphase cells using *Vysis ETV6/RUNX1 fusion* and deletion 13q FISH probe. The rest of the recurrent fusion markers, i.e., *ETV6/RUNX1, BCR/ABL1*, and *TCF3/PBX1* fusion were negative along with a negative status for MLL and IGH gene rearrangements (Figure 6).

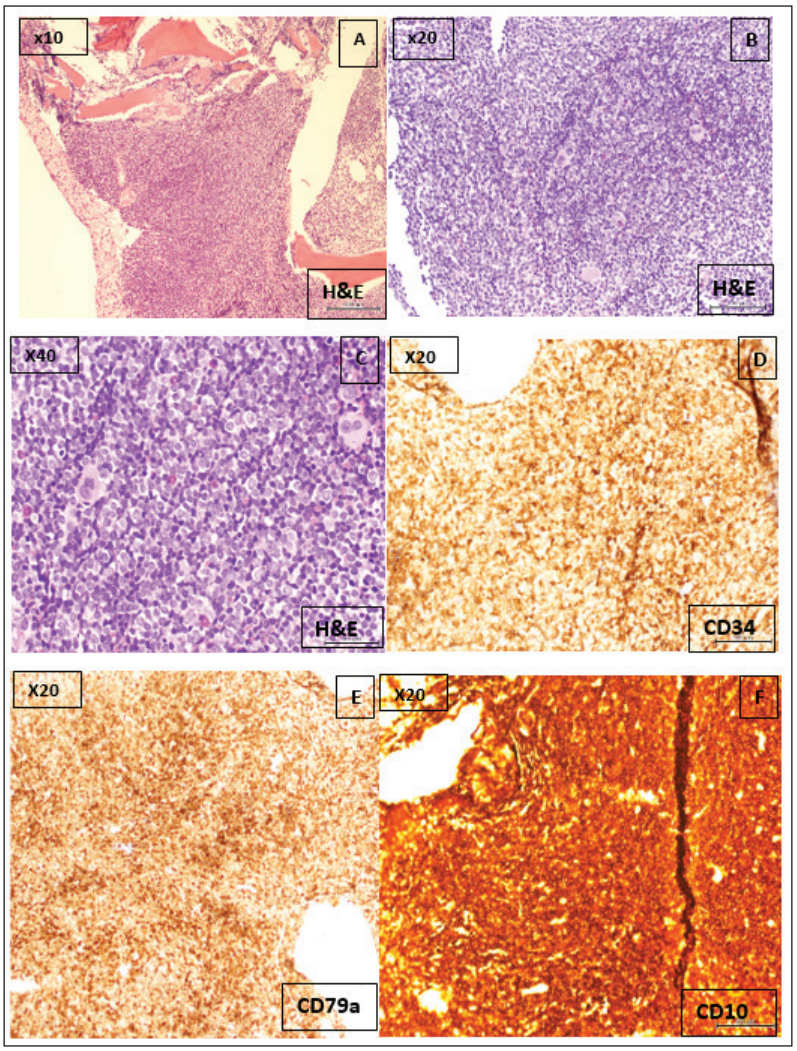

Figure 3. *Bone marrow trephine core biopsy slides showing markedly hypercellular bone marrow with diffuse infiltration by sheets of blast cells with high N/C ratio, open chromatin, and distinct nucleoli (A, B, C Hematoxylin and Eosin), immunostaining showed diffuse positive CD34 (D), CD79a (E), and CD10 (F), denoting B-Lymphoblasts.*

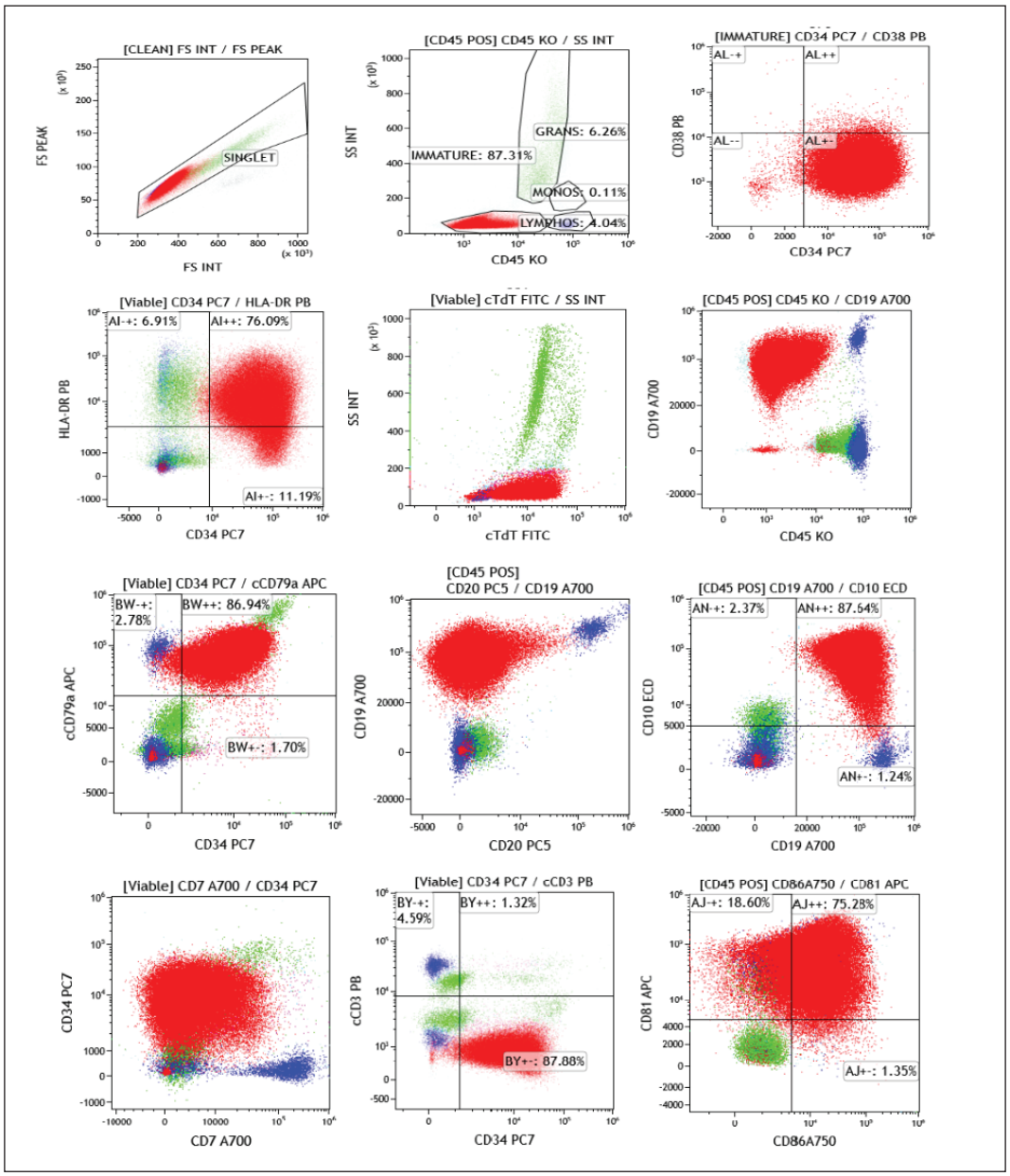

Figure 4. *Flow cytometry with immunophenotyping.*

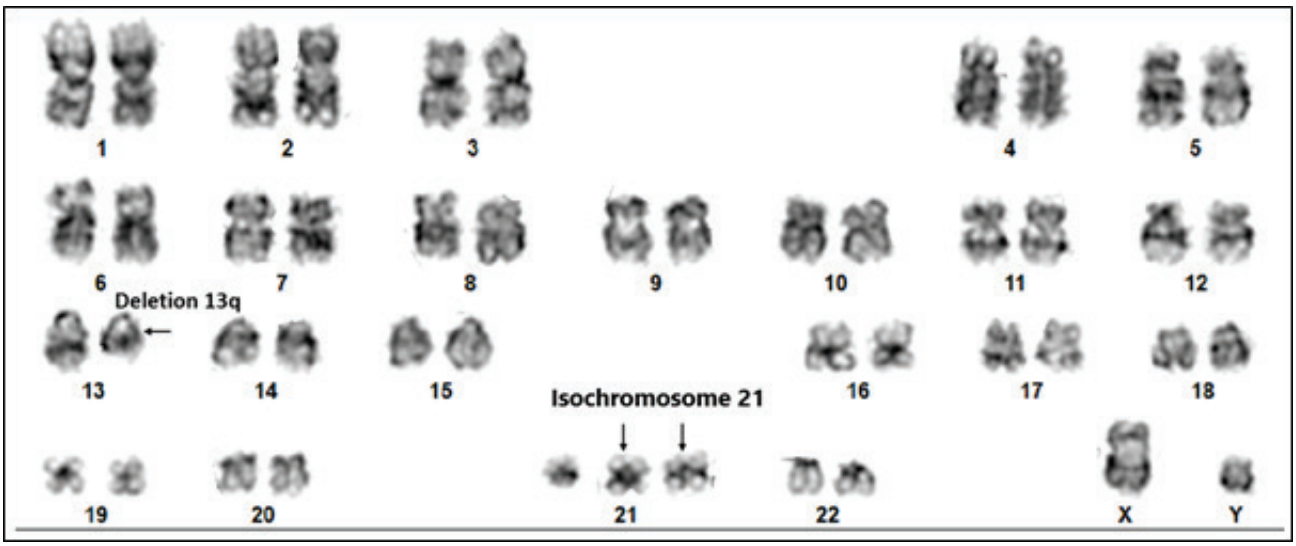

Figure 5. *Karyotype showing deletion 13q and duplication of derivative(21;21)(q10;q10).*

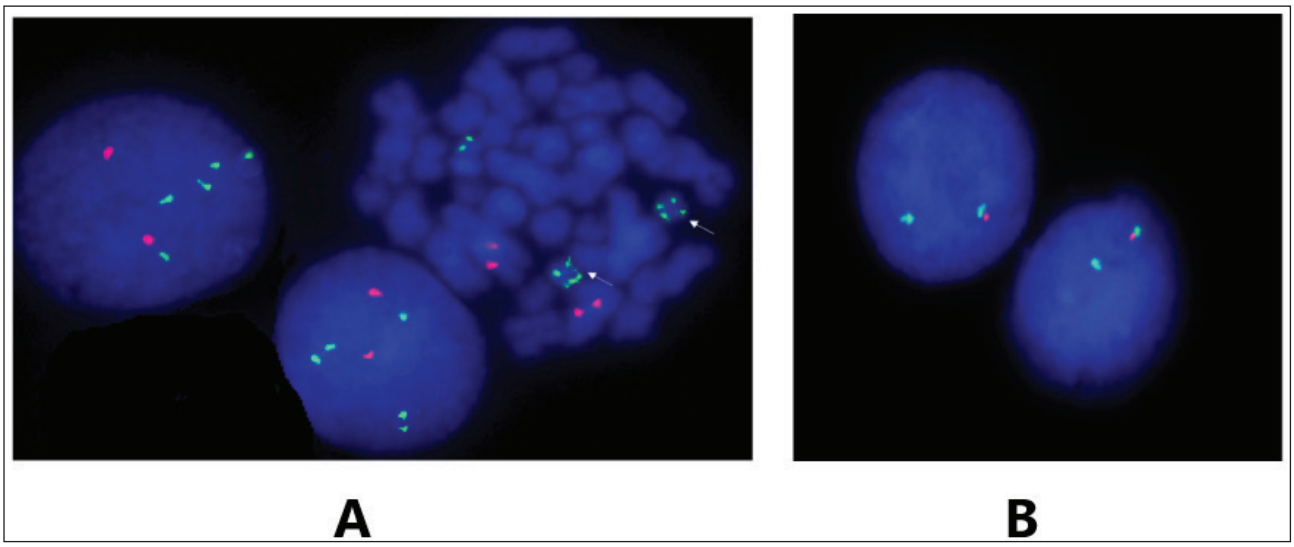

Figure 6A. *Interphase cells using ETV6/RUNX1 fusion probe showing 5 copies of RUNX1 (green) indicating extra copies of chromosome 21.* ***B****: Interphase cells with Deletion 13q probe showing 2 Green and 1 Red signal indicating interstitial loss of 13q14 region.*

Discussion

The co-occurrence of *der(21;21)(q10;q10)* and 13q deletions observed in the present case was a significant cytogenetic event, providing insight into the interplay of genetic alterations in leukemogenesis. The 13q deletions, especially those involving tumor suppressor genes like *RB1* near the *D13S319* marker, are known to drive tumorigenesis and are associated with poor prognosis, particularly in childhood ALL [8].

Pentasomy 21, arising from the duplication of the derivative chromosome *der(21;21)(q10;q10)* through isochromosome formation, represented a rare form of focal chromosome 21 hyperdiploidy. This leads to the amplification of oncogenes such as *RUNX1, ETS2*, and *ERG,* which possibly are contributed to hematopoietic dysregulation. While hyperdiploidy is typically linked to a favorable prognosis in ALL, tetrasomic abnormalities caused by endoreduplication are often associated with chromosomal instability and poor outcomes [9,10].

Literature study revealed similar chromosomal abnormalities across hematological malignancies, including ALL, AML, MDS, and transient myeloproliferative disorders in children with Down syndrome. Studies by Shimoyama et al. emphasized the role of duplicated isodicentric chromosomes in leukemogenesis via *RUNX1* amplification in AML [6,11].

Similarly, Vijay et al. [12] describe recurrent isochromosome 21 in complex AML karyotypes, underscoring its clinical relevance. Meanwhile, deletions in the *13q12-13q14* regions had been linked to leukemogenesis through the inactivation of tumor suppressors like RB1, crucial for cell cycle regulation, and mutations in *FLT3* that activate oncogenic pathways such as PI3K/AKT and RAS/MAPK. It was documented that in B-cell precursor ALL, deletions in the *13q12.2* region disrupt an enhancer upstream of *FLT3*, leading to increased *FLT3* expression and ligand-independent activation, which drives leukemogenesis [13].

This case represented the first reported coexistence of Pentasomy 21 (arising from *der(21;21)(q10;q10)*) with a 13q deletion in ALL. The amplification of chromosome 21 oncogenes and loss of 13q tumor suppressor functions created a unique cytogenetic profile that might synergistically drive leukemic progression. Although Pentasomy 21 is distinct from *iAMP21*, a well-recognized subtype of ALL associated with poor prognosis, the shared feature of 21q gene amplification, including key genes such as *RUNX1*, *ETS*, and *ERG*, highlighted a potential area for further investigation. The iAMP21's aggressive clinical course is driven by amplification-induced gene dysregulation, raising the question of whether Pentasomy 21 might exhibit overlapping leukemogenic mechanisms [14,15].

Pentasomy 21, involving the amplification of 21q genes, introduces the possibility of overexpression of critical oncogenes such as *RUNX1*, *ETS2*, and *ERG*, which are known to contribute to hematopoietic dysregulation and leukemic transformation. Simultaneously, the 13q deletion a cytogenetic aberration often linked to poor prognostic outcomes suggested an additional layer of genomic instability.

The coexistence of these abnormalities might have synergistic effects, amplifying leukemic pathways and influencing prognosis. For instance, 13q deletions disrupt tumor suppressor genes, which could work in tandem with the overexpression of 21q genes from Pentasomy 21 to accelerate disease progression. This unique cytogenetic combination highlighted the need for further studies to understand its impact on ALL pathophysiology and prognosis to address this co-existence of primary sole abnormality.

The co-occurrence of Pentasomy 21 and 13q deletions represented a novel finding, prompting investigations into their combined impact on clinical outcomes. While existing studies provide foundational knowledge of the co-existence, this case highlighted a need for understanding the precise leukemogenic mechanisms

underlying these cytogenetic abnormal co-occurrences. Further research is essential to elucidate their role in disease pathogenesis and prognostication. Evaluating clinical outcomes and therapeutic responses in similar cytogenetic profiles could provide valuable insights, ultimately guiding tailored treatment strategies for such rare cases.

List of Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BM	Bone marrow
CR	complete remission
FISH	Fluorescence *in situ* hybridization
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease

Conflict of interest

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent for publication

The permission was obtained from the patient to publish the case and the accompanying images.

Author contributions

All the authors listed in this article contributed to the acquisition of data from the patient, drafting and writing the manuscript along with final approval of this version to be published.

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