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Case Report

Cytogenetic Perspective on Paediatric AML: A Rare Case of t (1;12) (q24; q24.1) with Trisomy 21

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Abstract

Chromosomal translocations, such as the rare t (1;12) (q24; q24.1), play a key role in pediatric AML by disrupting critical oncogenes like BCL9 on chromosome 1q24 and tumor suppressors such as SH2B3 on 12q24. Trisomy 21 increases leukemia risk due to overexpression of genes including RUNX1 and DYRK1A. In this case, a 3-year-old boy showed aggressive AML features with high blasts, leukocytosis, anemia, and splenomegaly. Cytogenetic analysis confirmed the t(1;12) translocation and trisomy 21, while flow cytometry revealed myeloid blasts with aberrant CD7, indicating atypical immunophenotype. The SRSF2 gene mutation (p.P95H) found in this patient impairs RNA splicing, contributing to leukemogenesis, and the IKZF1 gene plays a critical role in hematopoietic differentiation and is associated with poor prognosis when mutated. This case highlights the importance of integrated cytogenetic and molecular diagnostics for understanding complex pediatric AML and guiding precise treatment.

Key words: cytogenetics; fluorescence in situ hybridization; trisomy 21; acute myeloid leukemia; giemsa -banding

Introduction

Chromosomal translocations form a key category of cytogenetic abnormalities leading to hematologic cancers through fusion gene formation, altered gene expression, or signalling changes that drive malignant transformation (Tomohiko Taki et al., 2006). Translocations involving chromosome 1 are among the most frequent in oncogenic activation, while chromosome 12q24 contains tumour suppressor and transcriptional regulation genes (Johansson, B. et al., 1997). Although t(1;12)(q24;q24.1) is rarely reported, genes within its breakpoints possess biological significance in leukemia (Fang, F. et al., 2022). The 1q21–1q24 region is dense with oncogenes relevant to hematologic malignancies, such as BCL9 at 1q21.2, a transcriptional coactivator promoting Wnt/β-catenin signaling (Leilei Chen et al., 2010). This pathway controls cell fate and survival, and its dysregulation is linked to multiple cancers, including leukemia. Translocations that upregulate BCL9 by juxtaposition to active regulatory elements cause oncogenic overexpression seen in several lymphoid malignancies (Song, P. et al., 2024). Elevated BCL9 augments β-catenin–mediated transcription, supports unchecked proliferation, and inhibits hematopoietic differentiation (Mani, M. et al., 2009). At 12q24.1, SH2B3 (LNK) encodes a negative regulator of cytokine signalling through the JAK-STAT pathway (Jiang, F. et al., 2016). Normally, SH2B3 restrains proliferation of hematopoietic progenitors by moderating cytokine effects like thrombopoietin and erythropoietin (Dale, B. L. et al., 2016). Its loss or mutation contributes to disorders such as MPNs, JMML, and acute Leukemia by enabling constitutive JAK-STAT signalling (Wintering, A. et al., 2024). NCOR2 (SMRT), another gene in this locus, acts as a transcriptional corepressor regulating chromatin remodeling via histone deacetylase recruitment (Privalsky, M. L. et al., 2019). Altered NCOR2 function has been linked to AML and other cancers by disturbing cell cycle and differentiation gene control (Trombly, D. J. et al., 2015). Cytogenetically, t(1;12)(q24;q24.1) can be visualized by G-banded karyotyping, while subtle rearrangements require molecular tools such as FISH and array-CGH (Peterson, J. F. et al., 2015). Probes targeting BCL9, SH2B3, or NCOR2 help confirm gene involvement, and RNA sequencing can reveal fusion transcripts (Hamid, F. et al., 2024). A BCL9–SH2B3 fusion could modify Wnt/β-catenin or JAK-STAT signalling, whereas BCL9–NCOR2 could impair chromatin repression, both potentially driving leukemic transformation (De la Roche et al., 2008; Lee, R. D. et al., 2022). Trisomy 21 results from nondisjunction producing a third chromosome 21 and causes genome-wide transcriptional imbalance (Antonarakis, S. et al., 2020). Overexpression of 21q22 genes drives Down syndrome phenotypes, with RUNX1 enhancing hematopoietic proliferation and Leukemia susceptibility (Haferlach, T. et al., 2019). DYRK1A triplication disrupts neuronal

signalling and contributes to cognitive impairment (Chu, D. et al., 2024). SOD1 overexpression increases oxidative stress and premature aging (Eleutherio, E. et al., 2021), while APP upregulation promotes early amyloid deposition and Alzheimer-like pathology (Wiseman, F. et al., 2015). Additional genes such as ETS2, RCAN1, and CBS influence apoptosis and metabolism in Down syndrome (Antonarakis, S. et al., 2020). Collectively, trisomy 21 alters cellular networks governing the cell cycle, mitochondrial function, immunity, and neurodevelopment, producing a distinct molecular signature (Letourneau, A. et al., 2014).

Case details:

A male child aged 3 years, presented to Paediatric Oncology Unit with suspected acute Leukemia. Peripheral smear and bone marrow study showed extreme leucocytosis, bad anaemia, thrombocytopenia, and predominant number of blast cells—up to 92% in bone marrow—establishing the diagnosis of acute leukaemia. Bone marrow aspirate was hyper cellular with inhibited erythropoiesis and megakaryocytes and positive Sudan Black B in some blasts, pointing towards myeloid lineage. Flow cytometry showed 50% marrow blasts expressing CD13, CD33, and CD117 (moderate), CD34 (dim), and aberrant CD7, while other T- and B-lineage markers were negative. These findings indicate acute myeloid leukaemia (AML) with aberrant T-cell marker expression, typically linked to poor-risk cytogenetics. Hematology revealed severe anemia (Hb 4.2–8.7 g/dL), thrombocytopenia (platelets 5–8 $\times 10^3/\mu L$), and leukocytosis (WBC up to 28 $\times 10^3/\mu L$). Serum LDH exceeded 1700 U/L, suggesting a high tumour burden. Liver and renal functions were normal, and ultrasound showed mild splenomegaly (10.3 cm) due to leukemic infiltration.

Next Generation Sequencing

A comprehensive NGS panel was performed on a whole blood sample from a 3-year-old male patient diagnosed with acute myeloid leukaemia (AML). The genomic analysis targeted multiple genes implicated in hematologic malignancies. The key findings include a pathogenic missense variant in the SRSF2 gene, p.(P95H) c.284C>A, with an allele frequency of 16.15%. This mutation is known to have adverse prognostic significance in AML according to ELN 2022 guidelines. Another missense variant in IKZF1, p.(A297S) c.889G>T, was detected with an allele frequency of 47.67%. No mutations were detected in other commonly altered genes such as FLT3, NPM1, TP53, RUNX1, and ASXL1. In summary, the patient was diagnosed with acute myeloid leukemia with immunophenotypic immaturity and aberrant expression patterns and a rare t(1;12)(q24;q24.1) translocation. The institutional review board approved the current study, and informed consent was provided by the patient.

Material and method:

Conventional Cytogenetics:

A G-banded chromosome analysis was conducted following a standard cytogenetic protocol. Bone marrow aspirate samples were cultured in RPMI-1640 medium enriched with 20% new-born calf serum, L-glutamine, and antibiotics (penicillin and streptomycin). The cultures were maintained at 37°C and incubated overnight with colcemid (10 µL per 8 mL of culture). Following incubation, the cells were treated with a hypotonic solution (0.075 mol/L KCl) and fixed using a methanol–acetic acid solution in a 3:1 ratio. Slides were prepared using the air-drying technique and subsequently stained using Giemsa banding. A total of 20 metaphases were examined, and karyotypes were interpreted in accordance with the International System for Human Cytogenetic Nomenclature 2020.

Whole Chromosome Painting FISH assay:

Whole Chromosome Painting (WCP) Fluorescence In Situ Hybridization (FISH) analysis was performed on metaphase spreads prepared from short-term cultured bone marrow cells. The procedure was carried out in accordance with the manufacturer's protocol (XCP, Metasystems). Whole chromosome painting (WCP) using probes for chromosomes 1 (Orange) and 12 (Green) was carried out to confirm a suspected t(1;12) translocation. Metaphase slides were denatured at 75°C and hybridized overnight at 37°C. Post-hybridization washes ensured specificity, and chromosomes were counterstained with DAPI for nuclear visualization. Fluorescent signals were analysed under a Zeiss AXIO Imager Z2 fluorescence microscope with a CCD camera, providing precise evaluation through both conventional cytogenetic and FISH techniques.

Result:

Conventional cytogenetic analysis by GTG banding on bone marrow cells revealed a clonal chromosomal abnormality with a translocation between chromosomes 1 and 12, noted as t(1;12)(q24;q24.1) in 16 out of 20 metaphases. Four metaphases showed a normal male karyotype (46, XY), indicating the presence of both abnormal and normal clones (Figure 1). Whole chromosome painting (WCP) FISH using probes for chromosomes 1 (orange) and 12 (green) demonstrated an abnormal fusion signal pattern indicative of a t(1;12) translocation. Orange fluorescence from chromosome 1 appeared on a predominantly green chromosome 12, confirming the transfer of genetic material between these chromosomes (Figure 2). The abnormal pattern was consistently detected in all 10 analysed metaphases, supporting the presence of a recurrent t(1;12) chromosomal translocation. To confirm the Trisomy of 21 FISH technique was used in which AML_ETO probe was used. AML1 gene is Present on Chromosome 21, which was labelled, with Green Fluorochromes while ETO gene is on Chromosome 8 labelled with Fluorochromes Orange.[In Figure 3, three green signals indicates the Trisomy 21.

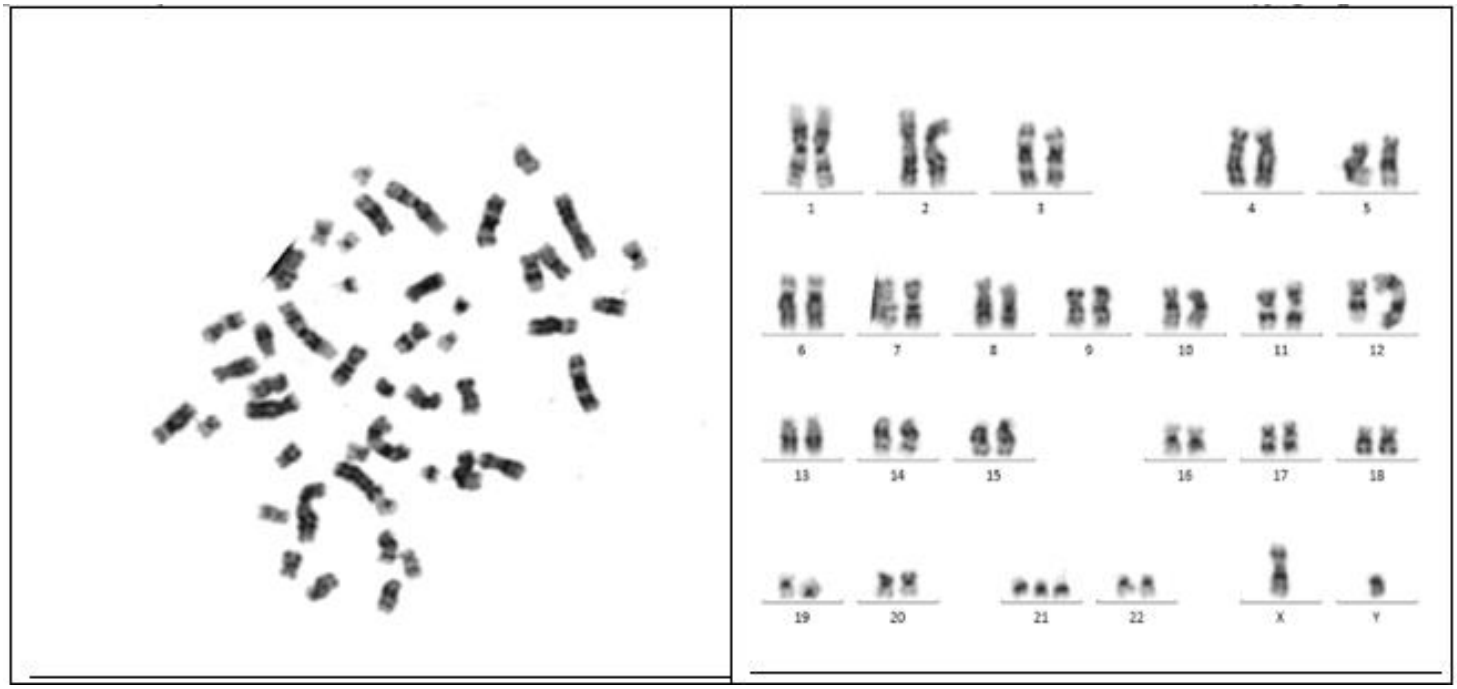

Figure 1: Representative images of Conventional cytogenetic results of GTG banded karyotype showing t (1; 12) (q24; q24.1) With Trisomy 21.

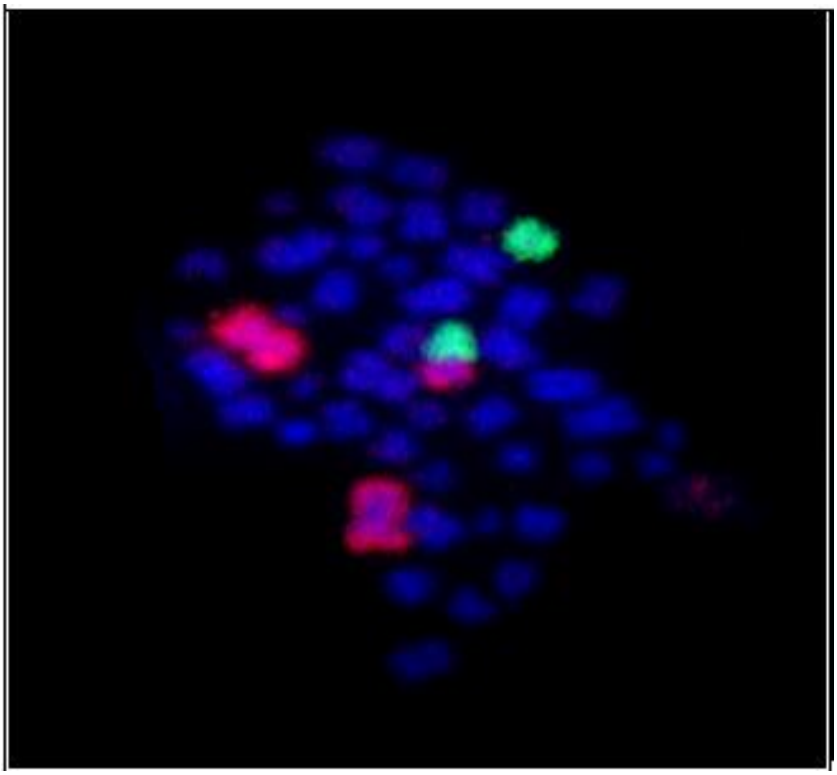

Figure 2: Representative images of WCP FISH in which Chromosome 1 was labelled with Fluorochrome Orange and Chromosome 12 was labelled with Fluorochrome Green

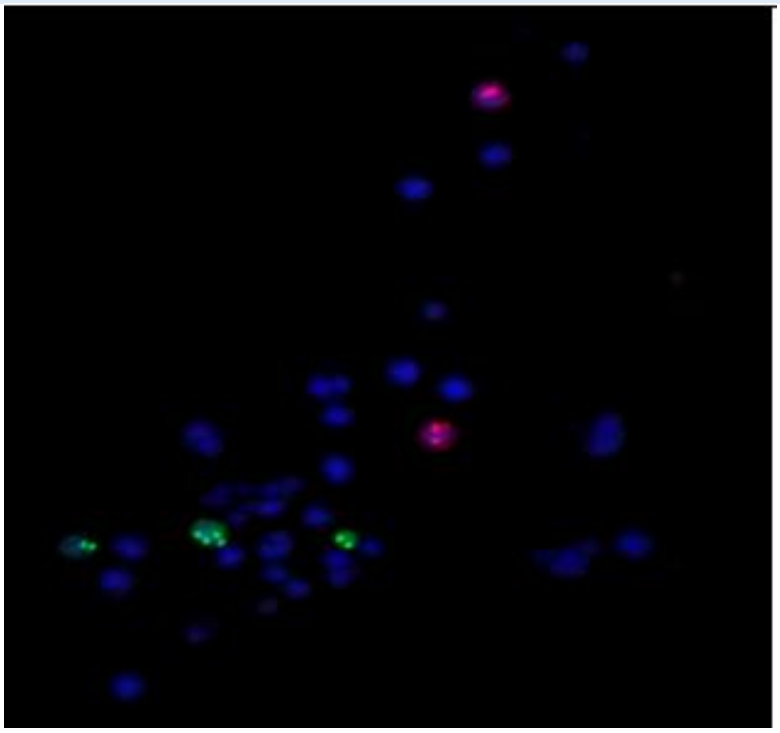

Figure 3: Representative image FISH in which Chromosome 21 was labelled with Fluorochromes green and Chromosome 8 with orange. 3 Green signal indicates trisomy of Chromosome 21

Discussion:

Childhood acute myeloid leukaemia (AML) is a pleomorphic malignancy with a variety of clinical presentation and varied cytogenetic abnormalities. Chromosomal translocations are central to the leukemogenesis in their ability to modify the expression or function of key regulatory genes required for haematopoiesis (Meshinchi, S., et al, 2007). In children with AML, recurrent translocations including t(8;21), inv(16), and t(15;17) are highly characterized and have prognostic and therapeutic implications (Rubnitz, J. E., et al, 2012). Yet, recognition of unusual or new structural lesions like t(1;12)(q24;q24.1), as noted in this case, emphasizes the continued requirement to understand further the complete range of cytogenetic variants that lead to leukemogenesis. This current case is a 3-year-old male who was diagnosed with AML and whose rare chromosomal translocation between the long arms of chromosomes 1 and 12 was noted. Routine cytogenetic study found t(1;12)(q24;q24.1) in most of the metaphases studied, which reflects a clonal abnormality. This result was also supported by Whole Chromosome Painting (WCP) FISH, which revealed the presence of chromosome 1 material on chromosome 12. The above structural rearrangement indicates a non-random and potentially pathogenic translocation between genes at or near the breakpoints on 1q24 and 12q24.1. From a molecular perspective, both of these chromosome regions involved in the translocation contain genes that are of functional importance in hematologic malignancies. The 1q21–q24 region, specifically, is a hot spot for structural alterations in a number of hematologic malignancies (Mitelman, F., et al, 2007). It contains BCL9, a known oncogene that functions as a co-activator for transcription in the Wnt/β-catenin pathway. Leukemogenesis has been implicated in BCL9 through mechanisms involving overexpression or fusion with enhancer elements, resulting in increased β-catenin activity and subsequent transcription of genes promoting cell proliferation, preventing apoptosis, and inhibiting differentiation. However, the direct implication of BCL9 in this particular instance is still to be molecularly confirmed, its location near the 1q24 breakpoint makes it a likely candidate for its dysregulation secondary to the translocation (Mala M. et al, 2009). Concurrently, chromosome 12q24.1 also harbours tumour suppressor genes including SH2B3 (LNK) and NCOR2 (SMRT), both of which are involved in the regulation of haematopoiesis. SH2B3 is an essential negative regulator of cytokine signalling through the JAK-STAT pathway and is a molecular brake on hematopoietic stem cell proliferation) (Fang, F., et al, 2022. SH2B3 loss-of-function mutations or deletions are commonly observed in myeloproliferative neoplasms and acute leukaemia. Disruption of SH2B3 may contribute to uncontrolled proliferation and survival of progenitor cells (Wintering, A., et al, 2024). Similarly, NCOR2 is a transcriptional corepressor that plays a role in chromatin remodelling and gene silencing. NCOR2 disruption has been documented in several malignancies, where it plays a role in leukemogenesis by inappropriate transcriptional regulation of genes related to the cell cycle and apoptosis (Mori T et al, 2021). The possible fusion or juxtaposition of genes like BCL9 and SH2B3 or NCOR2 in the context of t(1;12)(q24;q24.1) may have severe functional implications. Hypothetically, a BCL9–SH2B3 fusion would create a chimeric protein that aberrantly activates both Wnt and JAK-STAT pathways, resulting in aggressive leukemic transformation. Alternatively, translocation may cause relocation of enhancer elements to up-regulate oncogenic expression or suppress tumour suppressors irrespective of the generation of a fusion transcript (Rickman D. et al,2012). Trisomy 21 or Down syndrome is caused by the presence of an additional copy of chromosome 21 and thus overexpression of many genes that cause the clinical manifestations of the disorder. One of the genes most characterized to date is DYRK1A (dual-specificity tyrosine-phosphorylation-regulated kinase 1A). The gene has a central function in brain development and neuronal signalling pathways. Its overexpression has been associated with impaired neurogenesis, cognitive impairment, and structural brain abnormalities typically seen in patients with Down syndrome (Chu, D., et al, 2024). Another significant gene is DSCAM (Down syndrome cell adhesion

molecule), implicated in patterning neurons and synaptic contacts. The overexpression of DSCAM is thought to interfere with proper brain wiring during early life, causing intellectual disability and learning disorders. By the same the APP (amyloid precursor protein) gene, though on chromosome 21, also plays a role in the pathogenesis of early-onset Alzheimer's disease in Down syndrome. APP overexpression results in elevated levels of amyloid-beta peptides, which accumulate in the brain and create plaques typical of Alzheimer's pathology by the fourth decade of life (Tang, X., et al, 2021). The SOD1 (superoxide dismutase 1) gene is a gene encoding for an enzyme detoxifying reactive oxygen species. Although this protective function occurs in normal conditions, overexpression of SOD1 in Down syndrome creates an imbalance in oxidative metabolism with enhanced oxidative stress, which may damage tissues and cells, such as neurons (Eleutherio, E. et al, 2021). Moreover, the ETS2 gene, coding for a transcription factor implicated in controlling cell growth and apoptosis, has a potential to cause developmental abnormalities and immune dysregulation in an overexpressed state (Wilson, T. et al, 2003). RUNX1, at position 21q22.12, is a transcription factor required for regular haematopoiesis. RUNX1 controls the genes associated with differentiation and cell growth of the hematopoietic stem cells. In Trisomy 21, RUNX1 overexpression caused by gene dosage imbalance has been shown to be causative for leukemogenesis, especially in myeloid leukaemia of Down syndrome (ML-DS). RUNX1 is also a common target of chromosomal translocations in AML, like t(8;21), resulting in the oncogenic RUNX1-RUNX1T1 fusion. Dysregulation of RUNX1 impinges on transcriptional regulation, cytokine signalling, and epigenetic modifications and plays a pivotal role in leukemic transformation (Haferlach, T., et al, 2019). The SRSF2 gene encodes a serine/arginine-rich splicing factor that is essential for the regulation of pre-mRNA splicing, a critical step in gene expression. This protein recognizes and binds specific RNA sequences, facilitating spliceosome assembly and influencing exon inclusion or exclusion. Besides splicing, SRSF2 contributes to mRNA stability, export from the nucleus, translation, and maintains genomic stability (Mala M. et al, 2009). Mutations in SRSF2, particularly the hotspot mutation p.P95H, are commonly found in myeloid malignancies, including acute myeloid Leukemia (AML), where they cause aberrant splicing of key transcripts, disrupting normal blood cell development and contributing to disease progression. These mutations are also linked to poor prognosis, highlighting the gene's importance as a diagnostic and prognostic biomarker in haematological cancers (Fang, F. et al., 2022). Lastly, the IFNAR (interferon alpha-receptor) gene, which is a component of the immune system, is also triplicated in Down syndrome patients. Its overexpression can result in exaggerated immune response and contributes to the immune dysregulation of such patients in the form of heightened susceptibility to autoimmune diseases and infections (Zanin, N., et al, 2021). These genes and the imbalance in their dosage collectively contribute importantly to determining the phenotypic characteristics, health problems, and developmental delays that accompany Trisomy 21 (Antonarakis, S. et al, 2020). Clinically, the patient presented with high white cell counts, anaemia, thrombocytopenia, splenomegaly, and increased marrow blasts, indicating an aggressive disease. The immunophenotype suggested myeloid origin with aberrant CD7 expression, a feature linked to poor outcomes in AML. The rare t(1;12)(q24;q24.1) abnormality, along with these findings, signifies a high-risk profile. Although uncommonly reported, translocations involving 1q and 12q arms have been associated with adverse prognosis in hematologic malignancies (Ronaghy A. et al., 2021). Due to limited precedent, its prognostic impact remains uncertain, but the involvement of key oncogenic and tumour suppressor loci suggests a leukemogenic role. Molecular assays such as RT-PCR, RNA sequencing, or whole-genome sequencing could clarify its genetic and functional consequences (Mitelman, F. et al., 2022). This case highlights the importance of combining conventional karyotyping with advanced molecular cytogenetic methods like WCP FISH. While G-banding enabled preliminary detection of the structural abnormality, WCP FISH confirmed and clearly visualized the exchange of chromosomal material, enhancing diagnostic precision. Such integrated approaches are vital in clinical practice for uncovering subtle or cryptic rearrangements that may go unnoticed, especially in atypical cases of paediatric leukaemia.

Conclusion

This case in which AML with Trisomy 21 and uncommon t(1;12)(q24;q24.1) translocation indicates synergistic leukemogenic effect through gene dosage and structural changes. Gene overexpression of chromosome 21 genes like RUNX1 and DYRK1A predispose to leukemic transformation, whereas translocation presumably inactivates genes like BCL9 (1q24) and SH2B3 (12q24.1), which are implicated in Wnt signalling and hematopoietic regulation. This underscores the significance of combined cytogenetic and molecular profiling in knowing the genetic underpinnings of paediatric AML.

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