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Case Report

A New Complex Variant 4-Point Break Three-Way Translocation Involving Chromosomes 8, 15 and 17 in a Patient with Acute Promyelocytic Leukemia: A Case Report and Literature Review

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Abstract

The genetic hallmark of Acute promyelocytic leukemia (APL) is the balanced reciprocal translocation t(15;17)(q24;q21), resulting in the *PML::RARα* fusion gene. Although the majority of APL patients carry the typical t(15;17), variant translocations involving three or more chromosomes have also been described. We report a case of a 59-year-old man showing clinical, morphologic, laboratory, and immunophenotypic findings of APL. Cytogenetic analysis revealed a variant complex 4-point break-three-way translocation involving chromosomes 8p, 15q and 17q. Dual-color dual-fusion fluorescence *in situ* hybridization (D-FISH) analysis showed a typical pattern with two *PML::RARα* fusion signals, one on the derivative chromosome 17 and one on the derivative chromosome 8. Real-time quantitative reverse transcription polymerase chain reaction (RT-PCR) for *PML::RARα* transcripts was negative.

These results illustrate the usefulness of combining cytogenetic and molecular analysis to identify the *PML::RARα* fusion gene in all cases with strong suspicion of APL.

Keywords
Acute promyelocytic leukemia; *PML::RARα* fusion; complex variant translocation; karyotype; fluorescence *in situ* hybridization

1. Introduction

Acute promyelocytic leukemia (APL) accounts for approximately 10-15% of newly diagnosed acute myeloid leukemia (AML) cases, associated with life-threatening early bleeding and death [1-4]. The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has transformed APL from a highly fatal disease to a highly curable one. However, early death rates ranging from 8.2 to 32.6% remain a significant concern [3-6]. Therefore, prompt diagnosis and immediate initiation of appropriate therapy are critical.

The diagnostic hallmark of APL is the balanced reciprocal translocation t(15;17)(q24.1;q21.2) involving the promyelocytic leukemia (PML) gene located on chromosome 15q24.1 and the retinoic acid receptor alpha (RARα) gene located on chromosome 17q21.2, leading to the formation of the *PML::RARα* fusion gene [7-9]. The PML-RARA oncoprotein impairs normal myeloid differentiation and maturation, alters gene expression, deregulates transcriptional control, and inhibits apoptosis, playing a central role in the pathogenesis of APL and the differentiation response to ATRA [7-9].

Less than 10% of APL patients lack the classical t(15;17), but still harbor the *PML::RARα* fusion gene, as a result of insertional (cryptic or masked) events, or simple or complex variant translocations, involving chromosomes 15, 17 together with one or more additional chromosome(s) [10-36]. These rare *PML::RARα* rearrangements are difficult to diagnose, and their rapid identification is crucial for selecting the most effective treatment.

We report a previously undescribed complex variant translocation involving chromosomes 8, 15 and 17 in a patient with APL, who exhibited an unexpected typical fluorescence *in situ* hybridization (FISH) pattern and was negative by reverse transcription-polymerase chain reaction (RT-PCR).

2. Case Presentation

A 59-year-old man with no significant past medical history was referred to our institution in May 2025 for the evaluation and treatment of pancytopenia, detected on a routine blood test. Complete blood count revealed Leukopenia (White Blood Cells 1.4×10^9/L, Neutrophils 15%, Monocytes 14%, Lymphocytes 71%), Anaemia (Hb 9.3 g/dL, MCV 97.6 fL, MCH 36.6 pg), and Thrombocytopenia (PLT 20×10^9/L). The patient was asymptomatic and clinical examination was negative for lymphadenopathy or organomegaly. On admission, he underwent complete laboratory testing, peripheral blood smear examination, bone marrow aspirate, bone marrow immunophenotyping by Flow Cytometry, and cytogenetic analysis. In addition, DNA and RNA were extracted from the bone marrow sample for prospective molecular testing. Coagulation parameters were as follows: Prothrombin Time (PT) 14 sec (9.0-13.0), Activated Partial Thromboplastin Time (aPTT) 30.02 sec (26.00-38.00), Fibrinogen 2.33 g/L (2.00-4.50). Renal function, liver tests, and lactate dehydrogenase

(LDH) were within normal limits. Microscopic examination of the peripheral blood smear revealed the presence of rare atypical blastoid cells. Bone marrow aspirate was positive for the presence of a uniform blast cell population characterized by large cell size, intermediate nucleus-to-cytoplasm ratio, kidney-shaped nuclei, and coarse granules and occasionally Auer rods (Figure 1A). These morphological findings were indicative of APL. Consequently, molecular testing was requested specifically targeting the *PML::RARα* fusion transcript.

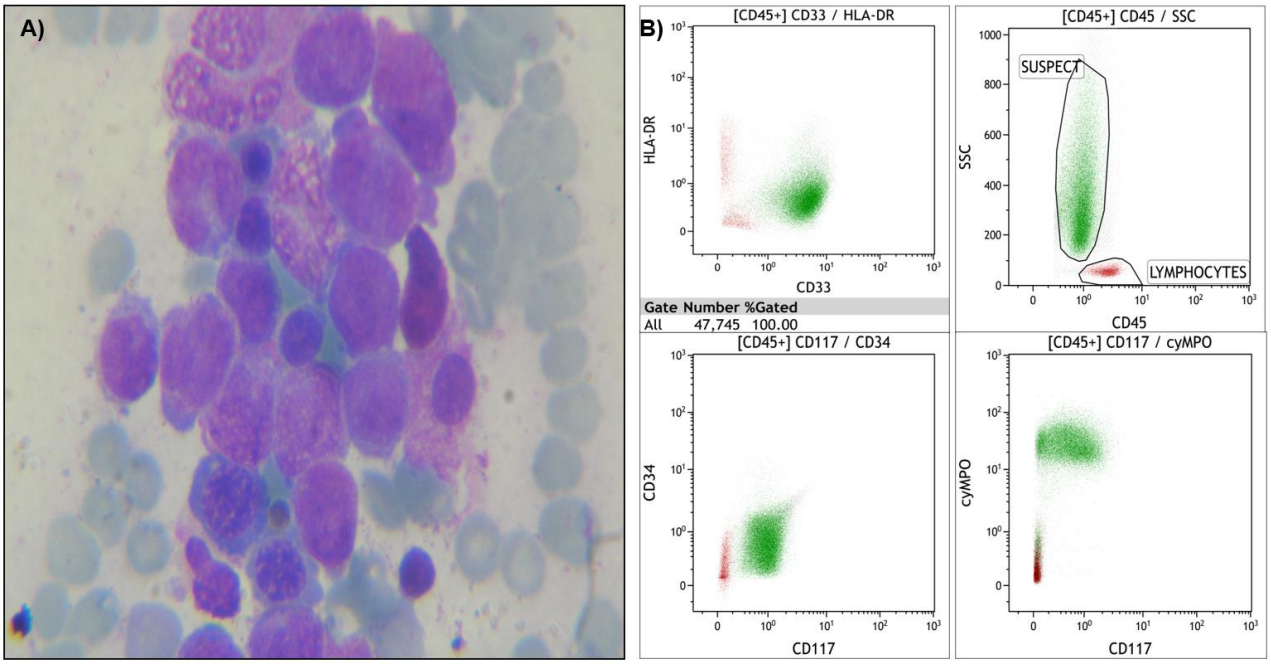

Figure 1 (A) Large-sized blast cells, intermediate nucleus-to-cytoplasm ratio, kidney-shaped nuclei, and presence of coarse granules and occasionally Auer rods; (B) Presence in the blast gate of a uniform population with increased granularity/intracellular complexity (SSC), expression of CD117, bright expression of CD33, cyMPO, and lack of expression of CD34 and HLA-DR.

Bone marrow immunophenotyping by flow cytometry revealed a homogeneous population of intermediate-sized cells with increased granularity/intracellular complexity and immunophenotypic characteristics $CD45^{+}CD34^{-}CD117^{+}CD13^{het}CD33^{++}HLA\text{-}DR^{-}MPO^{++}CD11b^{-}CD9^{+}$. The combination $CD9^{+}CD11b^{-}HLA\text{-}DR^{-}$ is considered to have 85% sensitivity and 95% specificity for classic APL, further confirming the suspicion of APL (Figure 1B). Per clinical guidelines, ATRA treatment was initiated immediately. Despite the negative molecular result for all three isoforms of the *PML::RARα* fusion transcript (L-bcr1, V-bcr2, S-bcr3), ATRA therapy was continued pending cytogenetic results because of the strong morphological and immunophenotypic evidence supporting the diagnosis of APL.

Conventional cytogenetic analysis was performed on 24 h and 48 h unstimulated bone marrow cultures using GTG (trypsin-Giemsa) banding at the time of his admission. Karyotypes were described according to the 2024 International System for Human Cytogenomic Nomenclature [37]. Among 24 metaphases analyzed, eight had a normal karyotype (46,XY), whereas 16 had a complex karyotype involving the long arms (q) of chromosomes 15 and 17 and the short arm (p) of chromosome 8 (Figure 2).

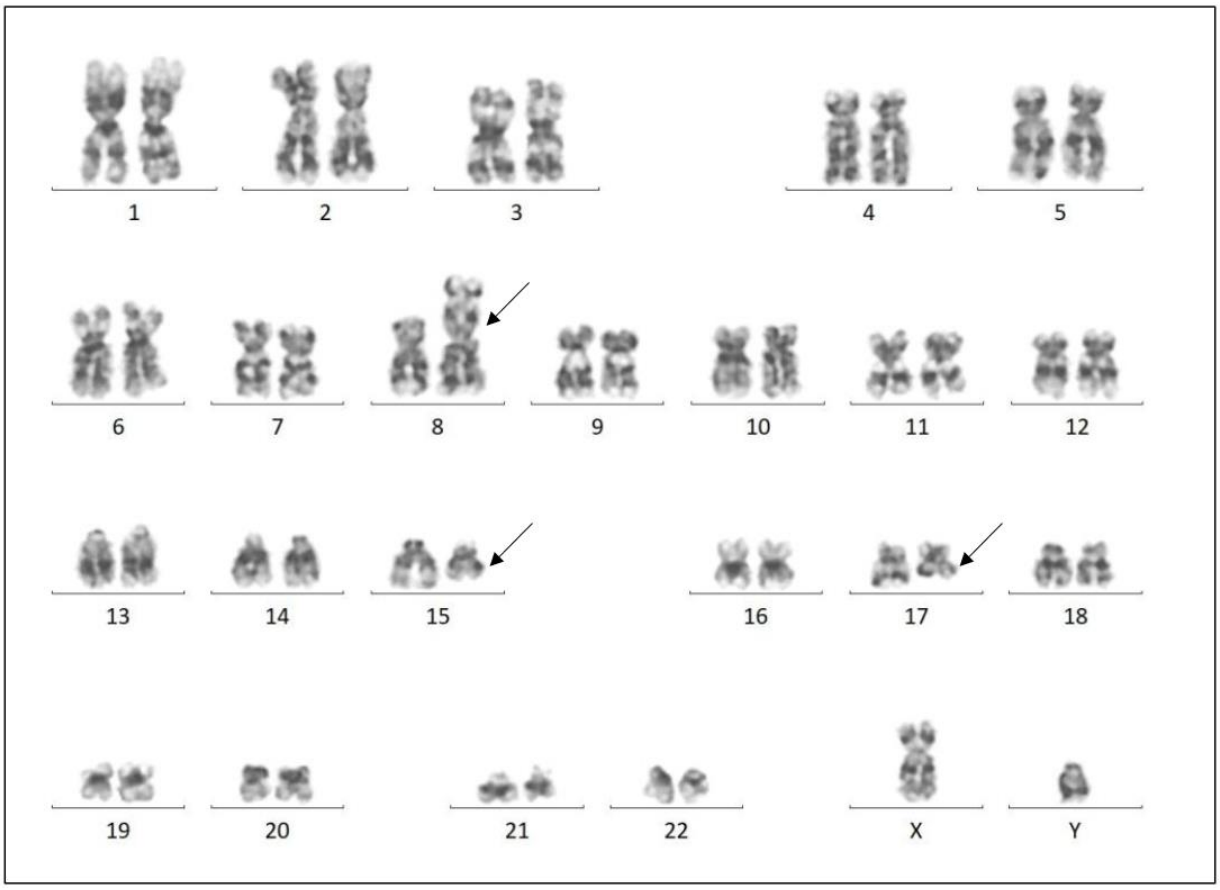

Figure 2 Complete karyotype showing 46,XY,der(8)t(8;15)(p23;q22)t(15;17)(q24;q21),der(15)t(8;15)(p23;q22)t(15;17)(q24;q21),der(17)t(15;17)(q24;q21).

Dual-color, dual-fusion (D-FISH) analysis was performed on 24 h unstimulated cells using the t(15;17) PML/RARA probe (Metasystems). Fluorescent signals were evaluated on metaphases and in at least 200 nuclei. Two *PML/RARA* fusion signals were detected in 166/200 (83%) interphase nuclei and in 5 metaphases analyzed, confirming the presence of the t(15;17)(q24;q21.2) translocation (Figures 3A, 3B). One *PML::RARα* fusion signal was located on the derivative chromosome der(17), whereas the second signal was detected not on the der(15), but on a larger chromosome (Figures 3A, 3B). Using XCE 8 enumeration and t(8;9)(p22;p24) PCM1/JAK2 dual-color, dual-fusion probes (Metasystems), two 8 chromosome centromeres, two 8p22 signals, and extra chromosomal material on one chromosome 8p were observed (Figures 3C, 3D).

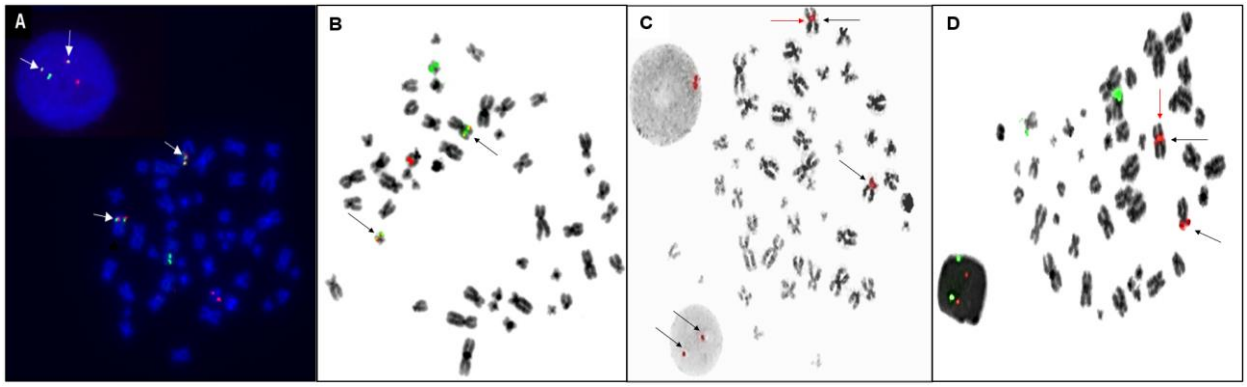

Figure 3 (A) FISH on a metaphase and on an interphase cell showing two PML/RARA fusion signals (yellow signals-arrows), one normal chromosome 15 (red signal) and one normal chromosome 17 (green signal), (B) Inverted-DAPI FISH analysis showing one PML/RARA fusion signal on the derivative chromosome 17 and the other PML/RARA fusion signal on a large chromosome, (C) Inverted-DAPI FISH on a metaphase and on two interphase cells showing 2 centromeres of chromosome 8 (red signals) and the presence of chromosomal material on one chromosome 8p, (D) Inverted-DAPI FISH on a metaphase and an interphase cell showing two chromosome 8p22 (red signals) and the presence of chromosomal material on one chromosome 8p.

Finally, the diagnosis of "Acute Promyelocytic Leukemia with *PML::RARα* fusion" was established. The patient was treated according to the PETHEMA LPA 2017 protocol (PETHEMA/PALG, Treatment of Acute Promyelocytic Leukemia, PETHEMA LPA 2017) and was classified as a low/intermediate-risk patient (WBC <10 × 10^9/L, age <70 years). However, due to a lack of ATO (Arsenic Trioxide), the patient followed the schedule of high-risk (≥60 years) patients. He started induction therapy with ATRA (45 mg/m^2/d) and Idarubicin (12 mg/m^2) on days 2, 4, 6, and 8. Triple consolidation therapy followed: course 1 with ATRA (45 mg/m^2/d × 15 days) and Idarubicin (5 mg/m^2/d × 4 days); course 2 with ATRA (45 mg/m^2/d × 15 days) and Idarubicin (8 mg/m^2 × 3 days); course 3 with ATRA (45 mg/m^2/d × 15 days) and Idarubicin (12 mg/m^2/d × 1 day), after the completion of which, monitoring of the disease was mandated by the protocol. Figure 4 provides a timeline of the treatments.

Figure 4 A timeline of the treatment showing dates of initial diagnosis, induction therapy, and triple consolidation treatment.

During induction, the patient had mild differentiation syndrome treated with corticosteroids. No cardiotoxicity was observed during the treatment period. Febrile neutropenia episodes occurred during the hematological toxicity period of each scheduled treatment scheme, but no evidence of bacteremia was detected.

In October 2025, the patient was in complete hematological, morphological, immunophenotypic and cytogenetic response. A repeat FISH analysis on bone marrow biopsy was negative for APL. In January 2026, the patient remained in complete hematological, morphological, immunophenotypic

and cytogenetic response, and repeat FISH analysis was negative. The next remission assessment is pending.

2.1 Ethics Statement

The Helsinki Declaration (1975) was complied with in the survey. Ethical approval was not required for this study in accordance with local/national guidelines.

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

3. Discussion

The formation of the *PML::RARα* fusion gene is the defining molecular event in APL, irrespective of whether it arises from the classic t(15;17) translocation or from atypical/variant rearrangements, or of its genomic location. Consequently, accurate identification of the fusion is of great importance for selecting the most effective and potentially life-saving treatment strategy [15, 16]. Currently, APL diagnosis is based on *PML::RARα* detection through immunophenotyping, conventional karyotyping, fluorescent *in situ* hybridization (FISH), real-time quantitative reverse transcription polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS). However, atypical/variant cases resulting from occult t(15;17) rearrangements remain diagnostically challenging and may remain undetectable.

Several atypical cases lacking the classic translocation t(15;17) have been described in APL, involving complex variant translocations that include chromosomes 15 and 17 together with one additional chromosome (three-way translocations) or more chromosomes (four-way translocations). Most autosomes, except chromosomes 14 and 21, and the X chromosome, have been reported to participate in these rearrangements [10-36]. Although there is no obvious clustering to particular chromosomal bands, the implication of putative oncogenes located in the breakpoint regions in the pathogenesis of APL is suggested [10, 11, 17-25, 34, 35]. According to the literature, patients with atypical APL exhibit comparable clinical features to those of typical APL, with an approximately equal male-to-female ratio and a median age at diagnosis of 45 years [38].

We present a patient with APL harboring a complex three-way translocation between chromosomes 8p23, 15q24 and 17q21. The involvement of chromosome 8 in three-way translocations associated with APL has been previously described, with several breakpoints implicated (p23, q11.2, q21.2, q22 and q24) [15, 22, 29]. The interesting thing in our case is the formation of a complex three-way translocation involving 4 breaks, two very closely spaced breakpoints on chromosome 15, one on chromosome 17 and one on chromosome 8. It is assumed that first, the typical, critical for APL, reciprocal translocation between 15q24 and 17q21 occurred, leading to the formation of two *PML::RARα* fusion signals on der(15) and der(17), followed by a second reciprocal translocation between der(15) with an additional breakpoint at 15q22, and chromosome 8p23, resulting in the formation of der(8) (Figure 5). Although the actual order of events cannot be confirmed, the observation of a single neoplastic clone carrying only the three-way translocation, without any detectable cells harboring the classical t(15;17), raises the possibility that the rearrangements occurred simultaneously rather than sequentially [16, 24].

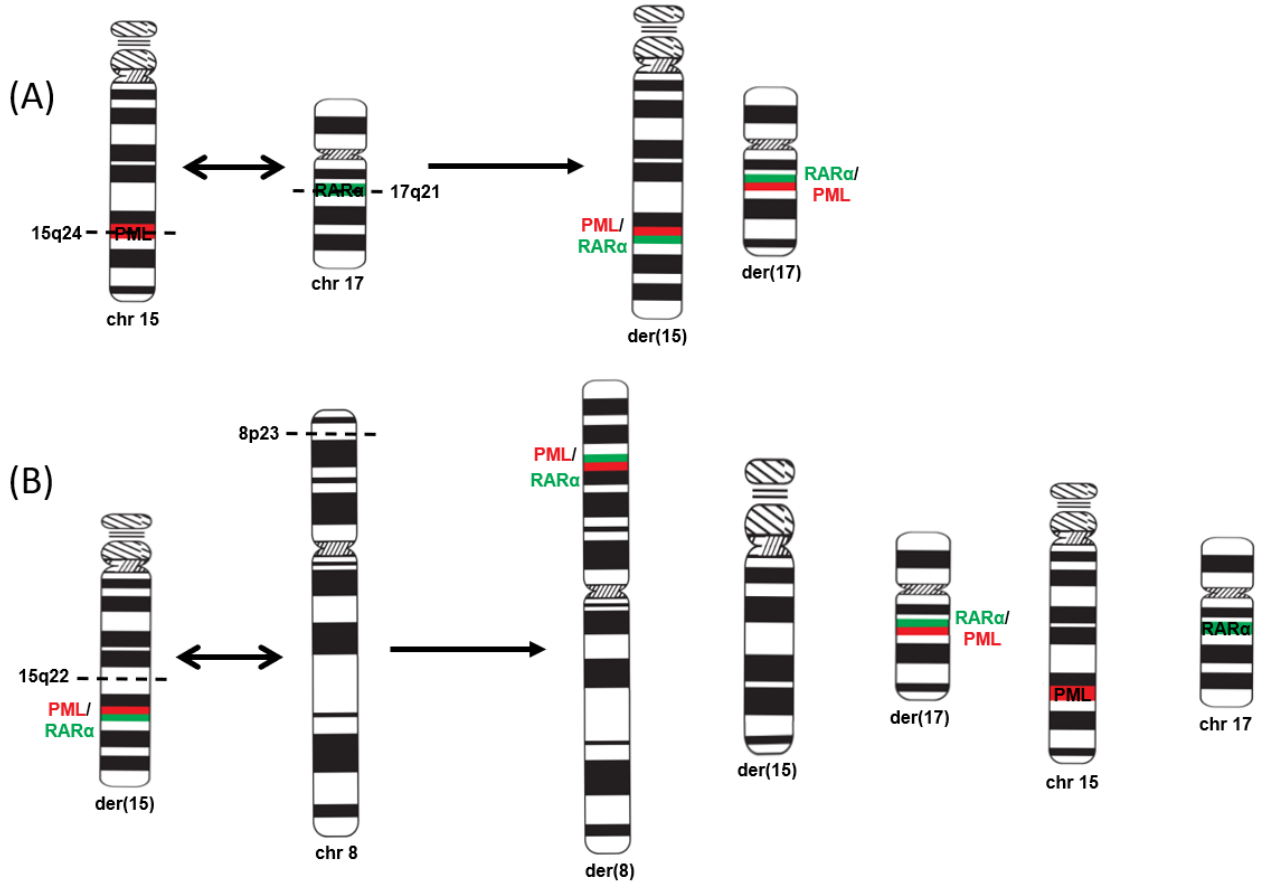

Figure 5 A 4-point break formation of the complex three-way translocation showing two sequential or simultaneous reciprocal translocations (A) the typical t(15;17), with breaks at 15q24 and 17q21, (B) the translocation between the der(15) and chromosome 8, with breaks at 15q22 and 8p23.

The above findings were confirmed by D-FISH analysis, which showed the typical signal pattern of one red, one green, and two fusion signals. One fusion signal was located on the der(17), whereas the second was detected on chromosome 8 rather than on der(15), due to the translocation between these two chromosomes. In most cases with complex variant translocations t(15;17), an atypical D-FISH pattern consisting of one fusion, two red and two green signals, usually results from a 3-point three-way translocation involving der(17) and a third chromosome [18]. One red and one green signal remain on the normal chromosomes 15 and 17, respectively; the single *PML::RARα* fusion signal is detected on der(15), while the reciprocal fusion signal is absent, because the corresponding red and green signals are separated and located on der(17) and the third chromosome (Table 1). Kim et al. (2023) reported a case in which one fusion signal was identified on der(17) and not on der(15), due to a complex three-way translocation involving 15q14, 15q24, and 17q21 [30]. Regarding the cases involving chromosome 8, D-FISH analysis was performed in four out of five patients, showing *PML::RARα* fusion signal on der(15), red signals on der(8) and the normal chromosome 15, and green signals on der(17) and the normal chromosome 17 [15, 22].

Table 1 Dual-color, dual-fusion FISH analysis of variant three-way translocations in APL patients.

Age (years)/sex	Karyotype	FISH pattern	Ref.
22/F	46,XX,t(5;17;15)(q11;q21;q22)	1F2R2G	Abe [19]
24/M	46,XY,del(15)(q15q22), der(17)t(15;17)(q22;q21)t(15;17)(q15;q21)	1F2R2G	Tirado [20]
57/F	46,XX,t(6;15;17)(q25;q22;q21)	1F2R2G	Eclache [21]
78/M	46,XY,t(3;17;15)(q27;q21;q22)	1F2R2G	Freeman [22]
49/F	46,XX,t(8;15;17)(q24.3;q12;q22)	1F2R2G	Freeman [22]
44/M	46,XY,t(15;22;17)(q22;q11.2;q21)	1F2R2G	Kato [23]
54/F	46,XX,t(15;16;17)(q24;q24;q21)	1F2R2G	Zhang [25]
33/M	46,XY,t(3;17;15)(q25;q21;q24)	1F2R2G	Wang [26]
19/F	46,XX,t(6;17;15)(p21;q21;q22),add(7)(q32)	1F2R2G	Zhang [27]
37/M	46,XY,t(1;17;15)(q21;q21;q24)	1F2R2G	Lv [28]
50/F	47,X,t(X;17;15)(p22.1;q21;q24),+8	1F2R2G	Gagnon [29]
43/M	46,XY,t(3;13)(q21;q32),t(3;17;15)(q23;q21;q24)	1F2R2G	Gagnon [29]
17/M	47,XY,t(4;17;15)(q31.3;q21;q24),+8	1F2R2G	Gagnon [29]
54/M	46,XY,t(7;17;15)(q22;q21;q24)	1F2R2G	Gagnon [29]
42/F	46,XX,t(7;15;17)(q34;q24;q21)	1F2R2G	Gagnon [29]
78/F	45,XX,-6,t(8;17;15)(p23;q21;q24),add(19)(p13.1)	1F2R2G	Gagnon [29]
30/F	46,XX,t(8;17;15)(q11.2;q21;q24)	1F2R2G	Gagnon [29]
58/F	46,XX,t(8;17;15)(q21.2;q21;q24)	1F2R2G	Gagnon [29]
60/F	46,XX,t(9;17;15)(p13;q21;q24)	1F2R2G	Gagnon [29]
79/M	46,XY,add(1)(p36.3),t(9;17;15)(p13;q21;q24)	1F2R2G	Gagnon [29]
31/M	46,XY,t(9;17;15)(q34;q21;q24)	1F2R2G	Gagnon [29]
23/M	46,XY,t(13;17;15)(q14;q21;q24)	1F2R2G	Gagnon [29]
19/F	46,XX,t(15;19;17)(q24;q13.1;q21)	1F2R2G	Gagnon [29]
40/M	46,XY,t(15;17;17)(q24;q11.2;q21)	1F2R2G	Gagnon [29]
59/M	46,XY,(15;15;17)(q24;q14;q21)	1F2R2G	Kim [30]
77/M	46,XY,t(2;15;17)(q21;q22;q21)	2F1R1G	Fujishima [16]
58/M	46,XY,t(12;15;17)(q24;q24;q11)	2F1R1G	Bennour [24]
-	47,XY,+8,t(7;17;15)(q22;q12;q22)	2F1R1G	Wan [18]
38/F	44-45,XX,t(14;15;17)(q32;q24;q21	2F1R1G	Gagnon [29]
50/M	46,XY,t(14;17;15)(q22;q21;q24)	2F1R1G	Gagnon [29]

To our knowledge, only a few cases exhibiting a typical D-FISH pattern have been reported to date (Table 1). Fujishima et al. (2000) and Bennour et al. (2013) described cases in which one *PML::RARα* fusion signal was abnormally located on der(2) and der(12), respectively, rather than on der(15) [16, 24]. Wan et al. (2007) showed a four-break, three-way translocation in which two *PML::RARα* fusion signals were detected on der(15) and der(7) [18]. Gagnon et al. (2022) reported two additional cases with a typical D-FISH pattern; however, no further information was provided [29].

Although both classical (karyotyping) and molecular (FISH) cytogenetics confirmed the presence of the *PML::RARα* fusion, RT-PCR was negative. In only two of five previously reported cases of three-way translocations involving chromosome 8 was RT-PCR performed, both were positive for *PML::RARα* transcripts [15, 22]. RT-PCR is a highly sensitive technique for detecting the three typical *PML::RARα* transcripts, due to different breakpoints within the *PML* gene: the long (L, or bcr1) transcript resulting from a breakpoint in intron 6, the variant (V, or bcr2) transcript involving exon 6, and the short (S, or bcr3) transcript resulting from a breakpoint in intron 3, involving 55%, 5%, and 40% of all t(15;17)-positive APL cases, respectively [38-41]. Rarely, variant *PML::RARα* translocations, insertions of genomic DNA sequences at the junction of the *PML* and *RARα* genes, or partial deletions of the *RARα* or *PML* genes, lead to atypical *PML::RARα* fusions, not readily identifiable using conventional primers [38-41]. These unknown breakpoints result in different *PML::RARα* transcripts, and their characterization and sequencing are important for understanding pathogenic molecular mechanisms and monitoring minimal residual disease (MRD). In our patient, a positive FISH result indicated the presence of the *PML::RARα* fusion gene, but RT-PCR was false-negative due to an atypical, novel breakpoint in the *PML* gene.

Our patient achieved complete hematological, morphological, immunophenotypic, and cytogenetic responses after treatment, suggesting that the abnormal localization of the *PML::RARα* fusion gene on chromosome 8 did not interfere with the clinical response to therapy. Cases with both typical and atypical PML-RARA isoforms have been correlated with diverse prognosis and responsiveness to treatments (e.g., ATRA), likely due to the different PML domains retained in the fusion protein [42]. However, studies have shown that the presence of the *PML::RARα* gene is crucial for achieving the best treatment response, regardless of its genomic location. No difference has been reported between variant and typical APL cases and according to the most recent recommendations, standard therapy should not be changed based on the PML-RARA isoforms [16-19, 23, 24, 35, 42].

Although traditional diagnostic techniques, such as karyotyping, FISH and RT-PCR, provide valuable information, they all have the limitation of incomplete genomic coverage [43]. NGS technology has fundamentally transformed the fields of genomics and molecular diagnostics by enabling rapid, cost-effective genetic analysis through methodologies, such as targeted gene panels, Whole Exome Sequencing (WES), and Whole Genome Sequencing (WGS) [43]. Unlike traditional sequencing methods, which are labor-intensive and limited in scope, NGS-based approaches enable the simultaneous sequencing of millions of DNA fragments and the comprehensive examination of the genetic landscape of leukemia [43]. NGS can detect a wide range of genetic alterations and has revolutionized the diagnosis, treatment, and minimal residual disease monitoring in leukemia [43]. However, high cost, complex data interpretation, and the lack of global standardization are limitations that currently prevent its universal adoption in clinical practice [43]. The final decision on conducting NGS in our case was driven primarily by financial constraints, as insurance providers do not cover this test.

4. Conclusions

Our findings demonstrate the first case of APL harboring a complex variant three-way translocation involving chromosome 8p23. The difficulty of identifying the *PML::RARα* fusion gene in APL patients with variant t(15;17) rearrangements involving uncommon breakpoints highlights

the importance of an integrated diagnostic approach combining morphology, immunophenotyping, classical (karyotyping) and molecular (FISH) cytogenetics, for optimal management of APL patients and better understanding of the pathogenesis of the disease. Further sequencing studies of both typical and atypical APL patients might shed light on the pathophysiology of the disease, the responsiveness to treatment and may aid in the development of novel targeted therapies.

Author Contributions

EK conceived, designed and supervised the study; EK and GB searched the literature and wrote the manuscript; EK, GB, MK, FD, IA performed the experiments and data analysis and interpretation. MD, E-FT: provided the clinical data. All authors revised and approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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