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Venetoclax-azacitidine treatment in *TTMV::RARA*-driven acute myeloid leukemia mimicking acute promyelocytic leukemia

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Authors' contributions.

ZL collected the clinical information of the patient and wrote the main text. ZZW, YBH, LLY, XY, CZZ, and LJ provided clinical data pertaining to the patient. HH, LQZ, and TK analyzed bioinformatics data. YZH and HGY revised the manuscript. YQH and SCJ were responsible for the initiation of the work.

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Data-sharing statement.

The datasets generated in this study are not publicly available due to ethical and privacy restrictions but are available from the corresponding authors upon reasonable request.

Short title: *TTMV*::*RARA* Treated with Venetoclax-Azacitidine

Scientific Category: Myeloid Neoplasia

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Disclosure/conflict of interest

The authors declare no conflict of interest.

Acute promyelocytic leukemia (APL) is typically defined by the presence of the *PML::RARA* fusion; however, rare RARA rearrangements can closely mimic APL while showing resistance to all-trans retinoic acid (ATRA).[1-3] Among these, torque teno mini virus (TTMV)::RARA fusion represents an exceptionally rare entity that is often undetectable by conventional assays.[4] To our knowledge, only a limited number of *TTMV::RARA* cases have been reported worldwide, and a consensus on optimal diagnostic and therapeutic strategies remains elusive. We report a case of APL-like acute myeloid leukemia (AML) driven by *TTMV::RARA* fusion, highlighting diagnostic challenges and a favorable response to venetoclax-azacitidine (VA) therapy. This case presents the first comprehensive evaluation of the efficacy of venetoclax combined with azacitidine in this molecular subtype, thereby addressing an important gap in the existing clinical evidence. A 71-year-old woman presented with fatigue, chest pain, and headache. On physical examination, the patient appeared acutely ill and had scattered petechiae and ecchymoses over the body. No palpable superficial lymphadenopathy was detected. Cardiopulmonary and abdominal examinations were unremarkable. Initial laboratory evaluation revealed pancytopenia, with a hemoglobin of 49 g/L, platelet count of 23 × 10^9/L, and white blood cell count of 4.15 × 10^9/L. Coagulation studies were consistent with disseminated intravascular coagulation, showing prolonged prothrombin time, fibrinogen level of 0.87 g/L, D-dimer >20.00 μg/mL, and fibrinogen degradation products (FDPs) >150.00 μg/mL. Peripheral blood smear demonstrated 78% abnormal promyelocytes with cytoplasmic granules and occasional Auer rods, strongly suggesting APL.

Bone marrow morphology was also consistent with APL (Figure 1A), and immunophenotyping analysis demonstrated strong CD117, HLA-DR, CD38, CD13, CD33, cytoplasmic myeloperoxidase (cMPO), CD371, and CD64 expression, whereas, CD45, CD11c, CD4, CD123, and CD56 were weakly expressed. However, reverse-transcription–polymerase chain reaction for *PML*::*RARA*, fluorescence in situ hybridization, and targeted fusion assays were all negative. Conventional karyotyping revealed a complex karyotype: 46,XX,idic(7)(q11.2)[14]/47,XX,+21[3]/46,XX[3], and targeted sequencing identified c.3144+1_3144+3del (NM_021140.4), a pathogenic *KDM6A* splice donor mutation that affects the splice donor site of exon 20. Despite these findings, a definitive diagnosis remained unclear. Whole-transcriptome RNA sequencing (RNA-seq) subsequently identified a *TTMV*::*RARA* fusion (Figures 2 and 3), establishing the diagnosis of *TTMV*::*RARA*-driven APL-like AML.

Given the initial suspicion of APL, treatment with ATRA and supportive care was initiated. Notably, coagulation parameters transiently improved after 2 days of ATRA therapy (PT, 15.2s; fibrinogen, 2.15 g/L; D-dimer, 19.5 μg/mL; and FDPs, 70.82 μg/mL), likely reflecting early ATRA-mediated differentiation; however, this response was neither sustained nor predictive of the underlying molecular disease biology. On the evening of day 5 after ATRA initiation, the patient developed acute chest tightness, dyspnea, and unexplained hypotension. At that time, peripheral blood smear examination revealed only reduction in the proportion of atypical promyelocytes to 28%. No

hypoxemia or oxygen desaturation was documented, and serial peripheral blood counts showed no evidence of hyperleukocytosis during this period; therefore, hydroxyurea was not administered for leukostasis prophylaxis. Chest radiography demonstrated no pleural effusion or bilateral interstitial infiltrates. Given the close temporal association with ATRA therapy and the exclusion of alternative cardiopulmonary etiologies, atypical differentiation syndrome (DS) was strongly suspected despite the absence of characteristic radiographic or laboratory findings. Consequently, ATRA was promptly discontinued, and empiric dexamethasone therapy was initiated. Because of persistent disseminated intravascular coagulation despite initial therapy, venetoclax plus azacitidine was initiated after 7 days of ATRA treatment. Coagulation parameters remained unimproved, with fibrinogen persistently low at 1.19 g/L, D-dimer remaininged elevated at >20 mg/L, and FDPs >150 μg/mL. Azacitidine was administered subcutaneously at 75 mg/m² daily on days 1–7, while venetoclax was administered via using a standard ramp-up schedule: 100 mg on day 1, 200 mg on day 2, and 400 mg daily on days 3-28. Follow-up bone marrow evaluation performed after completion of azacitidine therapy demonstrated a marked reduction in blasts (Figure 1B). Post-induction bone marrow examination performed 1 week after completion of VA therapy showed remission with trilineage hematopoiesis (Figure 1C), and flow cytometry confirmed minimal residual disease (MRD) negativity. The patient achieved complete remission (CR) and proceeded to consolidation therapy with VA. Regrettably, because of financial constraints, the patient has received only two cycles of VA therapy to date and has continued follow-up at the outpatient clinic of her local hospital. At the most recent follow-up on June 15 (6 months after diagnosis), the patient remained in hematologic remission with no evidence of disease relapse. The study protocol was approved by the Institutional Review Board (IRB) of the Zhuzhou Central Hospital Clinical Trial Center for Investigational Drugs (Approval No. KY2026019-01). Written informed consent was obtained from the patient for publication.

APL is classically associated with the *PML*:*RARA* fusion; however, approximately 5% of cases harbor alternative *RARA* partner genes, leading to heterogeneity in morphology, clinical presentation, and therapeutic response.[5] This case illustrates the diagnostic complexity of APL-like presentations lacking detectable *PML::RARA* rearrangement using standard assays. *TTMV*::*RARA* fusion, resulting from viral integration into the *RARA* locus, represents a rare and distinct subtype that was first described in 2021.[6] Emerging evidence, largely derived from pediatric cases, suggests that *TTMV*:*RARA*-associated leukemia may exhibit unique clinical features, including a potential for extramedullary involvement and relapse.[7] A landmark cohort study has previously characterized 29 *TTMV::RARA*-positive leukemia patients[8] and thoroughly summarized all previously documented cases of this rare subtype. The present case report focuses on highlighting the unique features of our patient, the oldest documented carrier of this fusion and expands the age, karyotypic, and therapeutic spectrum of this disease. In contrast to the predominantly pediatric cases described in that study,[8] our patient was a 71-year-old female who exhibited an atypical immunophenotype, had unique cytogenetic findings (idic(7)(q11.2) and trisomy 21), and achieved an MRD-negative CR that was maintained for 6 months after only two cycles of VA therapy without allogeneic transplantation. These observations further support *TTMV::RARA*-driven AML as a distinct, age-unrestricted disease

entity with heterogeneous genomic and clinical features.

Notably, *TTMV::RARA* remains undetectable by conventional diagnostic modalities, including *PML::RARA*-specific reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), and targeted next-generation sequencing (NGS) panels designed to detect known RARA fusion partners, thereby creating a critical diagnostic blind spot.[4] In contrast to other well-established RARA variant fusions (e.g., *NUP98::RARA*), which are often identifiable by cytogenetic analysis or targeted fusion assays,[9] *TTMV::RARA* requires transcriptome-wide approaches for reliable detection. We therefore propose RNA sequencing as a reflex test in morphologically suspected APL cases with negative *PML::RARA* results across on first-line assays. Adoption of this approach may improve diagnostic accuracy, reduce therapeutic delay, and facilitate timely treatment selection based on the underlying molecular driver.

This case further expands the genomic landscape of *TTMV::RARA*-driven leukemia. Although previous reports have frequently described isochromosome 17q (i(17q)) as a common cytogenetic abnormality in *TTMV::RARA*-positive cases,[7] our patient exhibited isodicentric chromosome 7 (idic(7)(q11.2)) and trisomy 21, abnormalities that are rarely observed in classical APL but are associated with high-risk AML, thereby adding further cytogenetic complexity to this subtype. Moreover, the concurrent loss-of-function *KDM6A* splice donor mutation c.3144+1_3144+3del (NM_021140.4), disrupting the splice donor site of exon 20, which has been associated with adverse prognosis in AML, represents the first reported co-occurring lesion in *TTMV::RARA* leukemia.[10] Available evidence suggests partial and transient sensitivity to ATRA and arsenic trioxide in *TTMV::RARA* cases, with high rates of early relapse and resistance.[8,11] Similarly, our patient demonstrated transient improvement in coagulopathy following empirical ATRA administration, which was subsequently followed by clinical deterioration and suspected DS, prompting discontinuation of ATRA therapy.

Treatment with the VA regimen induced an MRD-negative CR that was maintained for 6 months after only two cycles of VA in this patient. As reported by Boila et al.,[12] *KDM6A* loss enhances venetoclax sensitivity in AML through upregulation of BCL2 and downregulation of BCL2A1, mechanisms that may have contributed to the robust and sustained response to the VA regimen observed in this ATRA-resistant, high-risk setting. Consequently, the sustained MRD-negative CR achieved with VA is supported by a mechanistic rationale: venetoclax inhibits BCL-2-mediated resistance to apoptosis, whereas azacitidine promotes epigenetic reprogramming and restoration of myeloid differentiation.[13] This approach circumvents ATRA-dependent differentiation pathways and provides a rational therapeutic strategy for *TTMV::RARA*-positive AML with APL-like features and high-risk genetics. Given this favorable outcome, prospective evaluation of the VA regimen may be warranted.

The *TTMV::RARA* chimeric oncoprotein disrupts retinoic acid (RA) signaling and impairs myeloid differentiation, analogous to the canonical *PML::RARA* oncoprotein.[7] However, the early onset of

suspected DS in this patient suggests potential functional divergence between the two fusion proteins. Moreover, the presence of complex cytogenetic abnormalities and a loss-of-function *KDM6A* alteration may collectively contribute to intrinsic resistance to ATRA in this disease subtype.[10,14] In this case, the close temporal association with ATRA administration and the exclusion of alternative cardiopulmonary etiologies supported the clinical suspicion of atypical DS. This atypical presentation, lacking classic radiographic, hematologic, or serologic features, may reflect the distinct oncogenic properties of the *TTMV::RARA* fusion protein and co-occurring high-risk genomic alterations, which could contribute to divergent biological behavior and atypical treatment-related adverse effects compared with canonical *PML::RARA*-positive APL.

This study is limited by its single-case design. The pathogenesis of *TTMV*::*RARA* fusion, its impact on treatment sensitivity, and long-term prognosis remain to be clarified through additional cases and mechanistic studies. Furthermore, the potential interaction between the *KDM6A* mutation and the complex karyotype in disease initiation requires further investigation. Continued reporting of similar cases will be essential for improving clinical understanding and guiding therapeutic strategies.

References

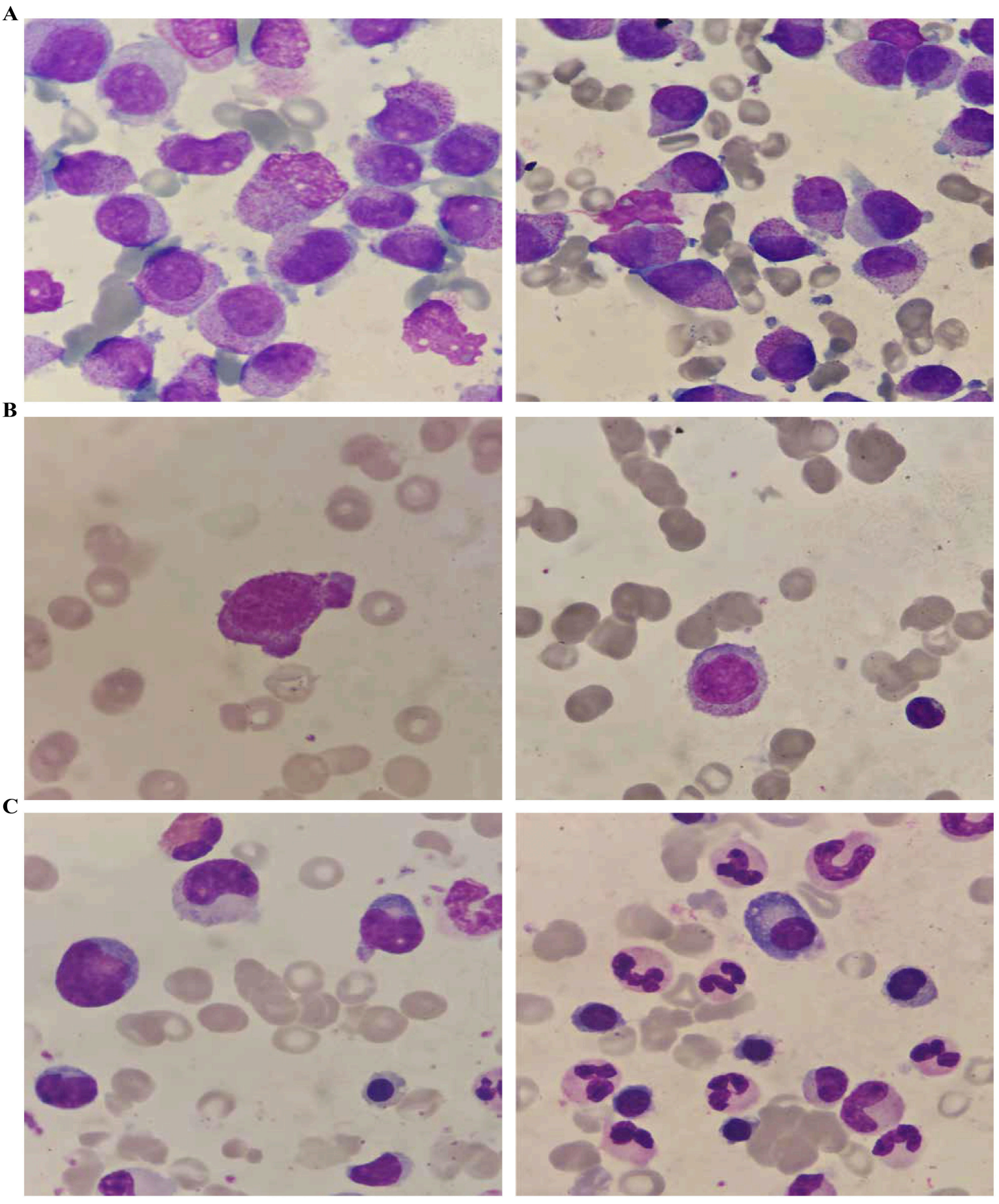
1. Winkler C. Acute promyelocytic leukemia. N Engl J Med. 2024;390(17):e42.
2. Jum'ah HA, Herrick JL. Acute myeloid leukemia with mutated NPM1 mimicking acute promyelocytic leukemia. Mayo Clin Proc. 2025;100(9):1575-1577.
3. Lin E, Chen W. Acute myeloid leukemia with NUP98::HOXA9 mimicking acute promyelocytic leukemia. Blood. 2023;142(21):1845.
4. Tsai HK, Sabbagh MF, Montesion M, et al. Acute promyelocytic leukemia with torque teno mini virus::RARA Fusion: an approach to screening and diagnosis. Mod Pathol. 2024;37(7):100509.
5. Mannan A, Muhsen IN, Barragán E, et al. Genotypic and phenotypic characteristics of acute promyelocytic leukemia translocation variants. Hematol Oncol Stem Cell Ther. 2020;13(4):189-201.
6. Astolfi A, Masetti R, Indio V, et al. Torque teno mini virus as a cause of childhood acute promyelocytic leukemia lacking PML/RARA fusion. Blood. 2021;138(18):1773-1777.
7. Sun S, Liu Y, Xu QY, et al. The comprehensive landscape of TTMV::RARA fusion-driven acute myeloid leukemia: from viral integration mechanisms to clinical outcomes. Haematologica. 2025;111(4):1254-1264.
8. Zhou X, Chen J, Tang YL, et al. Epidemiology, clinical features, and molecular basis of TTMV::RARA-driven acute promyelocytic leukemia. Blood. 2025;146(18):2229-2243.
9. Tu J, Wang H, Wang Y, Tong H. Identification of novel NUP98::RARA fusion transcripts in acute promyelocytic leukemia with i(17)(q10) abnormality. Am J Cancer Res. 2025;15(4):1932-1938.
10. Zhang S, Liu M, Yao Y, Yu B, Liu H. Targeting LSD1 for acute myeloid leukemia (AML) treatment. Pharmacol Res. 2021;164:105335.
11. Xu Q, Peng Y, Sun S, et al. Acute promyelocytic leukemia with TTMV::RARA fusion potentially responds to all-trans retinoic acid/arsenic trioxide treatment. Haematologica. 2025;110(6):1426-1431.
12. Boila LD, Ghosh S, Bandyopadhyay SK, et al. KDM6 demethylases integrate DNA repair gene regulation and loss of KDM6A sensitizes human acute myeloid leukemia to PARP and BCL2 inhibition. Leukemia. 2023;37(4):751-764.
13. Abdallah M, Xie Z, Ready A, Manogna D, Mendler JH, Loh KP. Management of acute myeloid leukemia (AML) in older patients. Curr Oncol Rep. 2020;22(10):103.
14. Ruijia L, Qianqian Z, Xiaohong L, Sen Y, Nan Z, Jing L. Acute promyelocytic leukemia with a novel TTMV::RARA fusion initially presenting as vertebral myeloid sarcoma: a case report. Front Oncol. 2026;16:1752011.

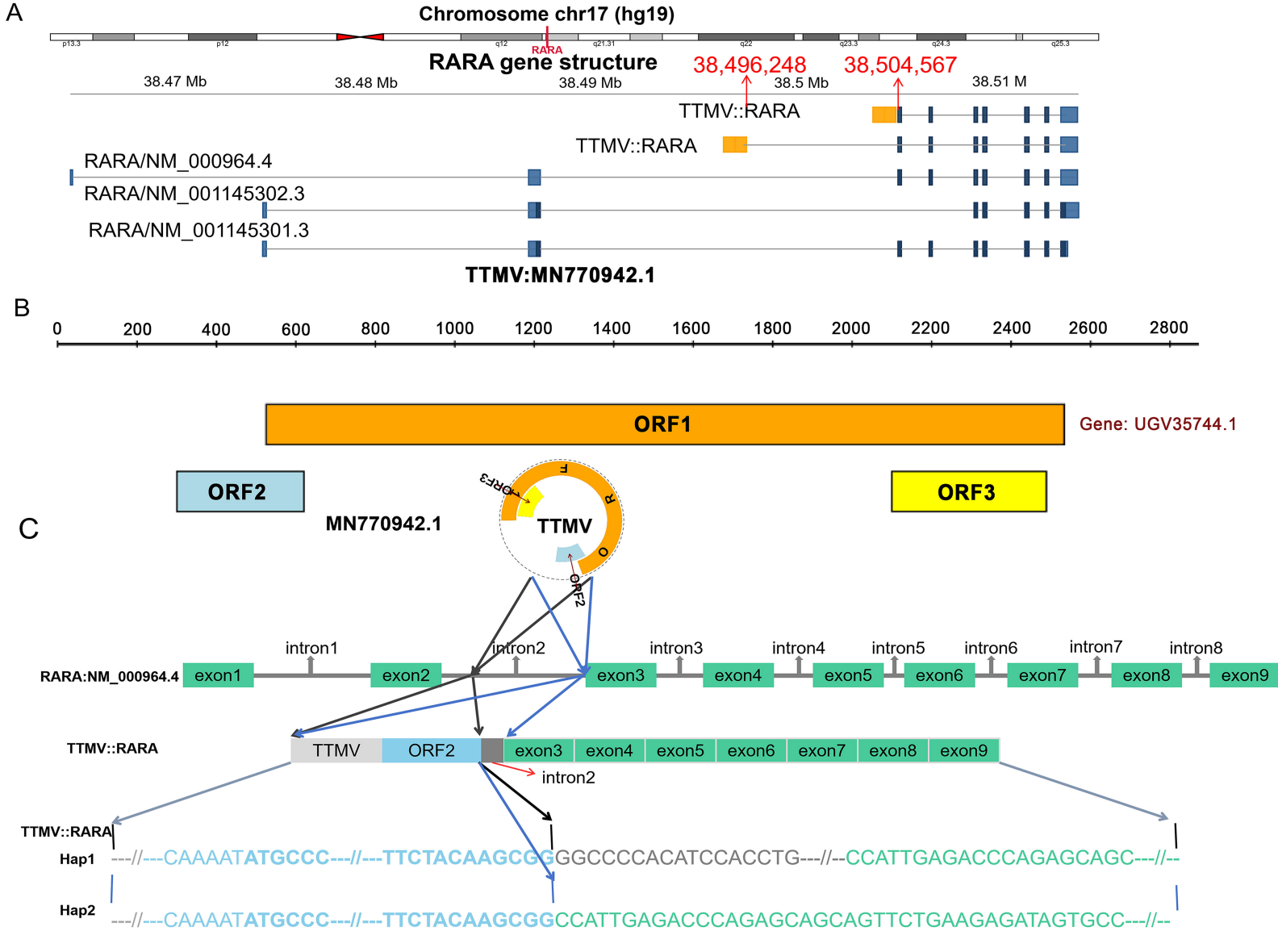
Figure legends

Figure 1. Bone marrow morphology at diagnosis and during treatment. (A) Bone marrow at diagnosis showing abnormal promyelocytes with acute promyelocytic leukemia (APL)-like features (Wright–Giemsa stain, ×1000). (B) After completion of azacitidine therapy showing reduced blast percentage. (C) After 1 week after completion of VA therapy showing remission with normal hematopoiesis.

Figure 2. Sequence features and integration schematic of the *TTMV::RARA* fusion transcript. (A) Coverage profile of the assembled fusion transcript across the RARA gene region based on the hg19 reference genome. (B) Coverage of the TTMV-derived sequence identified in this case mapped to the complete genome of TTMV isolate SAfiA-468-10. (C) Schematic representation of integration. The integration schematic depicts TTMV open reading frame 2 (ORF2) integrated into the RARA gene. The chimeric transcript comprises two isoforms: one contains the TTMV sequence joined to RARA from partial intron 2 to exon 9, and the other contains the TTMV sequence joined to RARA exons 3–9. The start codon (ATG) at the 5′ end of TTMV ORF2, or alternatively that of TTMV ORF1, may dominate the initial translation phase. Both isoforms were validated by bulk RNA-seq and Sanger sequencing.

Figure 3. Identification and characterization of the *TTMV::RARA* fusion by RNA sequencing. (A–D) Integrative Genomics Viewer (IGV) visualization and Sanger sequencing confirming the fusion breakpoints.


A
B
C


A
Chromosome chr17 (hg19)
RARA
RARA gene structure
38,496,248
38,504,567
38.47 Mb
38.48 Mb
38.49 Mb
38.5 Mb
38.51 M
TTMV::RARA
TTMV::RARA
RARA/NM_000964.4
RARA/NM_001145302.3
RARA/NM_001145301.3
TTMV:MN770942.1
B
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
ORF1
Gene: UGV35744.1
ORF2
ORF3
C
MN770942.1
TTMV
F
R
O
ORF3
ORF2
intron1
intron2
intron3
intron4
intron5
intron6
intron7
intron8
RARA:NM_000964.4
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exon2
exon3
exon4
exon5
exon6
exon7
exon8
exon9
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TTMV
ORF2
exon3
exon4
exon5
exon6
exon7
exon8
exon9
intron2
TTMV::RARA
Hap1
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Hap2
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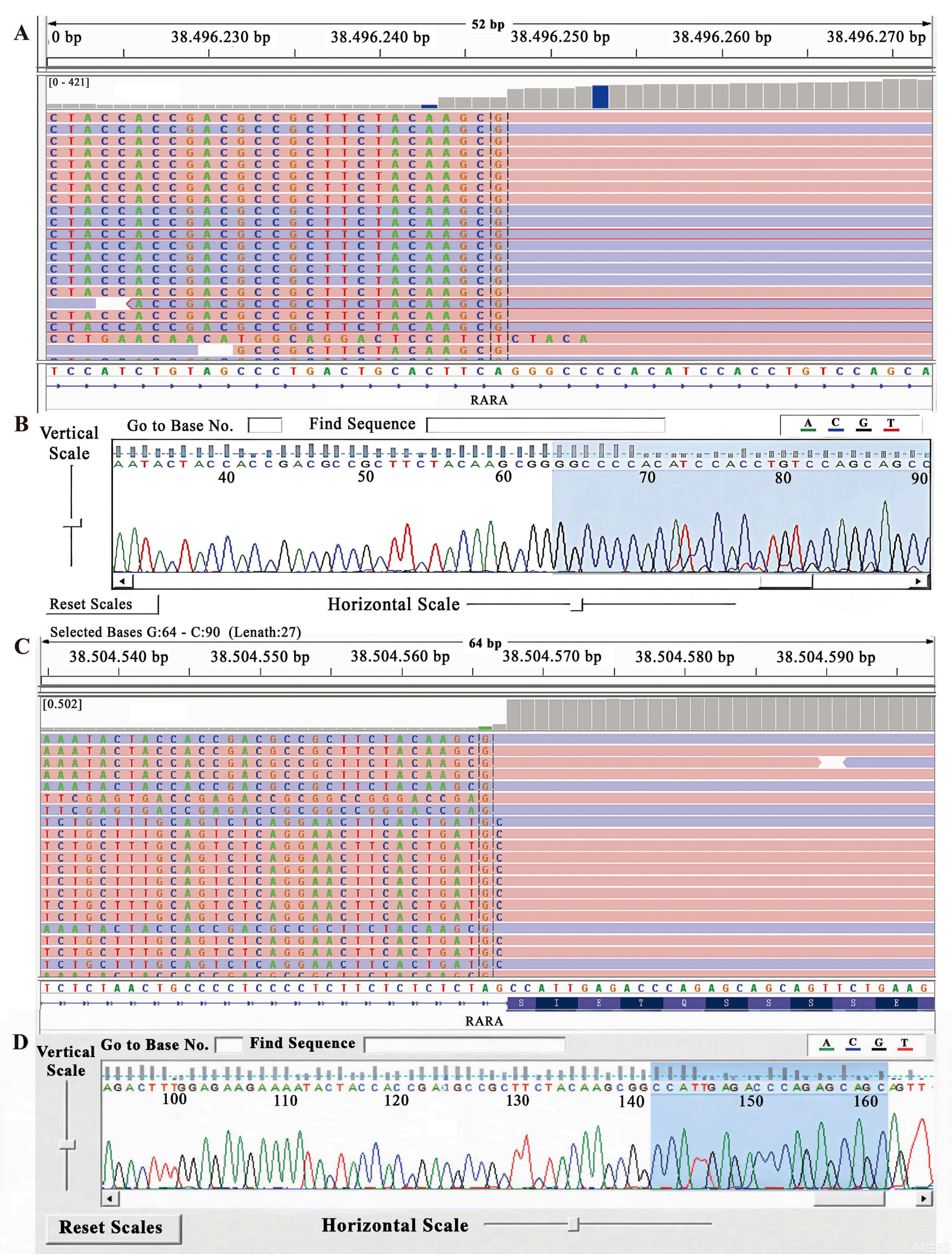
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RARA
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Go to Base No.
Find Sequence
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50
60
70
80
90
Reset Scales
Horizontal Scale
C
Selected Bases G:64 - C:90 (Lenath:27)
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RARA
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Go to Base No.
Find Sequence
A C G T
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110
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130
140
150
160
Reset Scales
Horizontal Scale