A Rare Case of Acute Myeloid Leukemia With ZBTB16-RARA (PLZF-RARA) Fusion: Diagnostic Challenges and Successful Morphologic Remission With CLIA + Venetoclax

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Introduction

Classic PML::RARA acute promyelocytic leukemia (APL) is highly curable with ATRA and ATO. In contrast, the rare ZBTB16::RARA variant retains APL-like morphology but is resistant to differentiation therapy and carries a high relapse risk. Recognizing its distinctive morphology may enable earlier diagnosis and appropriate intensive chemotherapy.

Clinical Presentation

PRESENTATION — NOV 20, 2025

31-year-old Hispanic man

No significant past medical history

Three weeks of progressive fatigue and generalized body heaviness

No fever, night sweats, weight loss, or bleeding

INITIAL LABORATORY FINDINGS

WBC	HEMOGLOBIN	PLATELETS
34.2 ×10³/µL 76% immature-like cells	7.7 g/dL	16 ×10³/µL

Mild coagulopathy: PT 14.6 s • INR 1.3

PERIPHERAL BLOOD FLOW CYTOMETRY — NOV 25, 2025

90.1% **MYELOBLASTS**

EXPRESSED

CD13 • CD33 • partial CD34 • CD117

ABERRANT CD56 • CD2 • CD15 **NEGATIVE** CD38 • HLA-DR

DIAGNOSTIC BONE MARROW — DEC 1, 2025

CELLULARITY	BLASTS	RETICULIN FIBROSIS
99%	75%	MODERATE

FISH RARA rearrangement + • trisomy 8 + • PML::RARA –

NGS **ZBTB16–RARA fusion**

WT1 LOF (VAF 45.4%) • SMARCB1 LOF (VAF 44.4%)

FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; LOF, loss-of-function; VAF, variant allele frequency.

Treatment Course

DEC 12, 2025 — **KEY COMPLICATIONS** — **FEB 17–23, 2026**

INDUCTION

CLIA + venetoclax

Cladribine • idarubicin • cytarabine

- Venetoclax administered in triturated form after swallowing difficulty
- Tumor-lysis prophylaxis: hydroxyurea, allopurinol, and IV fluids
- Aggressive transfusion support: PRBCs • platelet apheresis • cryoprecipitate
- Mediport placed December 18, 2025

KEY COMPLICATIONS

- Profound neutropenia — ANC <50
- Maculopapular rash → **TMP-SMX → atovaquone**

RE-INDUCTION

Second cycle of CLIA + venetoclax completed

Discharged in stable condition

WBC 6.0 ×10³/µL | Hgb 11.7 g/dL | Platelets 132 ×10³/µL

CLIA, cladribine–idarubicin–cytarabine; ANC, absolute neutrophil count; TMP-SMX, trimethoprim–sulfamethoxazole.

Figures

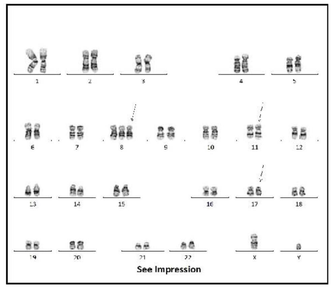

Image 1 — Diagnostic karyotype: Abnormal male karyotype:45,X,−Y,t(11;17)(q23;q21)[13]/47,idem,+8[7]. Arrows show t(11;17) at 11q23–17q21 and trisomy 8.

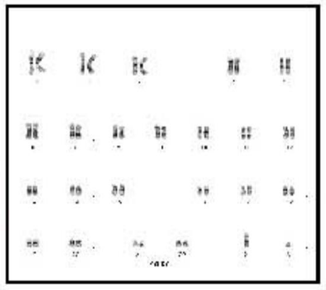

Image 2 — Post-induction karyotype: Normal male karyotype: 46,XY[20]. t(11;17) and +8 are no longer present after CLIA + venetoclax.

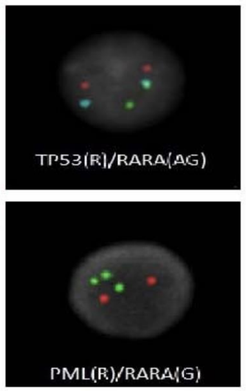

Image 3 — RARA FISH (top) and PML::RARA FISH (bottom): Top: split RARA signals = RARA rearrangement (79% of cells). Bottom: no fusion signal = PML::RARA (-).

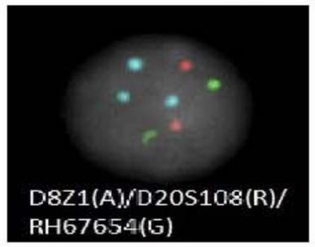

Image 4 — Chromosome 8 FISH: Extra aqua D8Z1 signals confirm trisomy 8.

Bone Marrow Response

DATE	CELLULARITY	BLASTS	KEY FINDINGS
Dec 1, 2025	99%	75%	ZBTB16–RARA positive; trisomy 8; fibrosis grade 1–2/3
Jan 14, 2026	95%	6%	Partial response; normal karyotype; flow negative for high-grade disease
Mar 16, 2026	40%	3% by IHC	**Morphologic remission** Normal karyotype; NGS negative for Tier I–III variants

IHC, immunohistochemistry; NGS, next-generation sequencing.

Clinical Pearls

1 SUSPECT A VARIANT FUSION

APL-like morphology with negative PML::RARA testing should prompt evaluation for alternative RARA rearrangements.

2 ANTICIPATE RESISTANCE

ZBTB16::RARA is typically resistant to ATRA and ATO; intensive AML-directed chemotherapy is often required.

3 CONFIRM MOLECULARLY

Molecular testing is essential because morphology and immunophenotype may closely resemble classic APL.

4 ASSESS RESPONSE BROADLY

Integrate marrow morphology, flow cytometry, cytogenetics, and NGS when evaluating treatment response.

Conclusion

ZBTB16::RARA AML is a rare, ATRA/ATO-resistant leukemia requiring molecular confirmation to guide therapy. In this patient, CLIA plus venetoclax induction and re-induction produced a progressive reduction in marrow blasts from 75% to 3%, culminating in morphologic remission. Venetoclax-containing intensive regimens may represent a promising approach, although continued molecular monitoring and consideration of consolidation or allogeneic transplantation remain essential.

References

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