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Case Report

A Case Report of Cryptic Acute Promyelocytic Leukemia with Atypical Features

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Abstract

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) characterized by unique biological and clinical features. Historically classified as AML-M3 in the French–American–British system, APL is defined by the t(15;17)(q24.1;q21.2) chromosomal translocation, which generates the *PML::RARA* fusion gene. Rare cases lacking t(15;17) but harboring a RARA fusion detectable by polymerase chain reaction (PCR) are referred to as cryptic APL, and such cases pose a diagnostic challenge. We report an unusual case of cryptic APL lacking the t(15;17) translocation and without typical APL symptoms/signs in preceding months, finally exhibiting numerous promyelocytes with Auer rods on repeated blood and bone marrow examinations. Despite the absence of t(15;17), a low level of *PML::RARA* was detected in next-generation sequencing and PCR. Additional cytogenetic analysis revealed trisomy 8. The patient was successfully treated with a combination of all-trans retinoic acid and arsenic trioxide. Complete hematological and molecular remission was achieved smoothly. This case highlights the diagnostic complexity of cryptic APL, emphasizing the importance of integrating genetic testing, morphological evaluation, and clinical assessment.

Keywords: Acute promyelocytic leukemia, case report, cryptic, *PML::RARA*

Introduction

Acute promyelocytic leukemia (APL) accounts for approximately 5%–20% of cases of acute myeloid leukemia (AML) and is classified as APL with t(15;17)(q24.1;q21.2)/*PML::RARA* and APL with other *RARA* rearrangements.[1,2] Studies have shown that *RARA* breakpoints consistently occur in intron 2, whereas breakpoints in the *PML* gene can occur at three distinct sites: intron 6, exon 6, or intron 3. These lead to the formation of three different *PML::RARA* isoforms – bcr1 (long), bcr2 (variant), and bcr3 (short), respectively.[3] This clearly illustrates how the *PML::RARA* fusion gene plays an important role in the pathogenesis of APL. The t(15;17)(q22;q12) translocation

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can be detected by conventional cytogenetic methods in about 70%–90% APL patients. However, a small subset of patients appear cytogenetically normal but are eventually confirmed to have APL, known as "cryptic" APL.[4-6] The most common clinical presentation in patients with APL is coagulopathy.[7] Treatment with all-*trans*-retinoic acid (ATRA) has shown a good response, achieving a complete remission rate of 90%.[8]

We report a patient with the initial presentation of neutropenic fever and persistent pancytopenia lasting for 3 months, with an inconclusive diagnosis despite two bone marrow biopsies. His karyotype showed 46, XY, +8. We finally identified the *PML::RARA* fusion using next-generation sequencing (NGS) and reverse transcription polymerase chain reaction (RT-PCR). The patient achieved complete remission after receiving treatment for APL.

Case Report

A 41-year-old man with a past medical history of gastric ulcer presented to our hematology and oncology outpatient department (OPD) for evaluation of pancytopenia. He was independent in activities of daily living and had maintained his usual health status until approximately 4 months before admission.

In April 2024, he was admitted to *A* Hospital with pancytopenia and neutropenic fever. Initial laboratory data showed a white blood cell (WBC) count of 1500/μL, hemoglobin (Hb) level of 11.3 g/dL, platelet count of 92,000/μL, creatinine (CRE) level of 0.8 mg/dL, and GOT level of 23 U/L. His fever resolved following antibiotic therapy. A subsequent bone marrow examination at *B* Hospital revealed hypercellularity without a definitive diagnosis. He was then referred to *C* Hospital in June 2024, where a repeat bone marrow biopsy demonstrated hypercellularity with mild myeloid dysplasia, whereas erythroid and megakaryocytic lineages appeared normal. Cytogenetic analysis identified trisomy 8 (+8) in 1 of 25 cells; however, the *BCR::ABL* test was negative. No conclusive diagnosis was made at that time.

On August 7, 2024, he was referred to our Hematology and Oncology OPD for further evaluation of persistent pancytopenia. Laboratory findings at that time showed a WBC count of 6730/μL, Hb level of 8.9 g/dL, and platelet count of 16,000/μL. Notably, 60% of promyelocytes with frequent Auer rods were observed [Figure 1]. The D-dimer level was elevated at 5525 ng/mL.

A bone marrow examination on August 7, 2024, confirmed the diagnosis of APL (AML-M3) [Figure 2]. Molecular studies, including NGS, detected the *PML::RARA* transcript at 8.89% (*PML::RARA* read count = 28,789, total RNA mapped read count = 323,923). However, cytogenetic analysis did not reveal the classical t (15;17) translocation but showed trisomy 8 in 2 of 18 metaphase cells [Figure 3]. He was diagnosed with cryptic APL and classified as intermediate-risk APL based on hematologic findings. Induction therapy was initiated

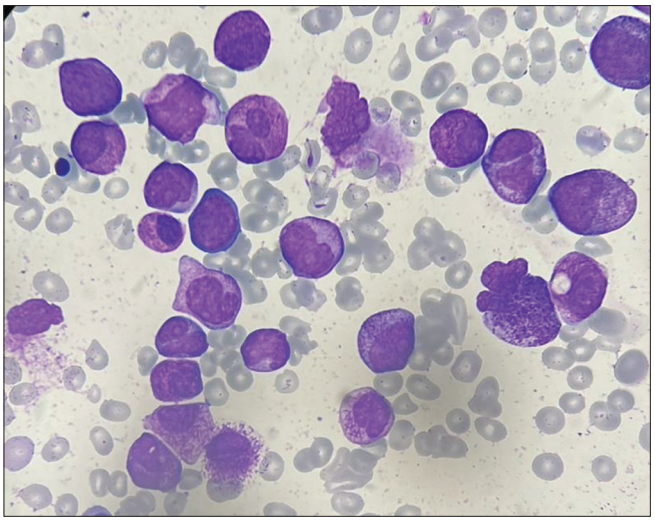

Figure 1: Promyelocytes with Auer rods

with ATRA, 45 mg/m^2/day from August 8, 2024, and arsenic trioxide (ATO), 0.15 mg/kg/day from August 10 to September 6, 2024. Following induction therapy, hematologic parameters normalized. A follow-up bone marrow examination on September 5, 2024, showed no abnormal promyelocytes and hematological complete remission, although *PML::RARA* PCR revealed minimal residual disease (MRD) at 1.35%.

Adverse effects included Grade I hepatitis attributable to ATO, which was managed conservatively. The patient received consolidation therapy with ATRA and ATO, following a schedule of 5 days on and 2 days off. On October 25, 2024, follow-up PCR testing revealed a serum *PML::RARA* level of 0.000%, indicating molecular complete remission. He finished consolidation therapy in March 2025, and the last PCRtest revealed no MRD.

No significant clinical bleeding was found in the preceding 4 months before the diagnosis of APL or after the initiation of ATRA plus ATO treatment. The treatment course was uneventful after being diagnosed with APL, and ATRA-related differentiation syndrome did not occur.

Discussion

APL is a distinct subtype of AML characterized by the t(15;17)(q24;q21) translocation, which leads to the formation of the *PML::RARA* fusion gene.[1] The genetic hallmark is typically detectable through conventional cytogenetic methods. However, a rare subset of APL cases, known as cryptic APL, lacks the visible t(15;17) translocation but still harbors the *PML::RARA* fusion, which can only be identified through advanced molecular techniques. These cases pose a significant diagnostic challenge due to their atypical cytogenetic profile. Mohebnasab *et al*. reported a series of 55 cases of cryptic APL, comprising 20 males and 35 females with a median age of 42.5 years (range: 10–68), comparable to that of typical APL patients whose median age is approximately 47 years.[9]

Our patient was a 41-year-old male who presented with persistent pancytopenia and intermittent fever over several months without significant bleeding. Initial bone marrow examinations revealed hypercellularity with mild dysplasia, and cytogenetic analysis identified trisomy 8 without the classical t(15;17). The absence of definitive cytogenetic abnormalities delayed the diagnosis. It was only upon subsequent evaluations, including the emergence of abnormal promyelocytes in the circulation, NGS, and RT-PCR, that the *PML::RARA* fusion gene was detected, confirming a diagnosis of cryptic APL.

Cryptic APL is rare, accounting for <10% of all APL cases, and is characterized by typical promyelocytic morphology.[6] The diagnosis of APL often relies on advanced molecular techniques, as conventional methods such as karyotyping and fluorescence *in situ* hybridization (FISH) may fail to detect cryptic rearrangements.[10] NGS and RT-PCR have been shown to be more sensitive in identifying these hidden genetic abnormalities, underscoring the importance of incorporating molecular diagnostics in cases with high clinical suspicion but negative cytogenetic findings.[11,12] The European Working Party reported that cryptic APL may involve complex rearrangement mechanisms, including three-way and simple variant translocations.[6] In Mohebnasab *et al*.'s review of 55 cryptic APL cases, 39 of the 55 patients were negative for the *PML::RARA* fusion by FISH, whereas all were positive by RT-PCR.[9] In our patient, conventional karyotyping failed to detect the rearrangement, but both NGS and RT-PCR revealed a positive *PML::RARA* fusion. Kim *et al*. suggested that certain FISH probes may miss the *PML::RARA* fusion due to small insertional events being masked by strong fluorescent signals. Rarely, RT-PCR may also fail to detect such fusions due to transcript variability.[12] These findings highlight the importance of combining morphologic assessment with cytogenetic and molecular tools such as FISH and RT-PCR to ensure an accurate and timely diagnosis of APL.

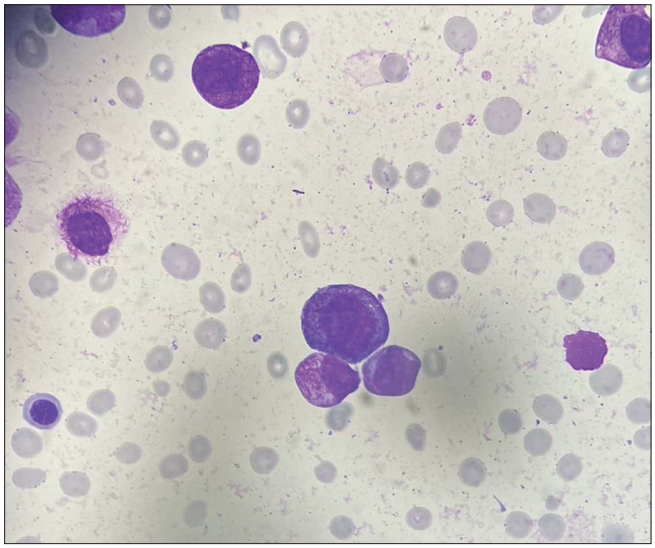

Figure 2: Promyelocytes with Auer rods, high power field

The presence of trisomy 8 as an additional chromosomal abnormality was noted in our patient. A case series of 54 patients with typical APL reported between 1979 and 1996 suggested that the presence of additional chromosomal abnormalities may be associated with poorer prognosis.[13] In another study of 37 patients, Goldschmidt *et al*. identified trisomy 8 as the most frequent additional chromosomal aberration in APL.[11] Similarly, a study from a Spanish group reported trisomy 8 as the most common secondary cytogenetic abnormality, observed in 14 of 113 patients with or without the classical t(15;17) translocation.[14] Interestingly, the study also demonstrated that such secondary cytogenetic changes did not adversely affect treatment outcomes or prognosis in newly diagnosed APL patients who received ATRA and idarubicin followed by anthracycline-based consolidation. These findings are consistent with those from the APL 93 trial, which showed no significant prognostic impact of additional chromosomal abnormalities.[15] Furthermore, in a phase 3 trial, the combination of ATRA and ATO was shown to be non-inferior,

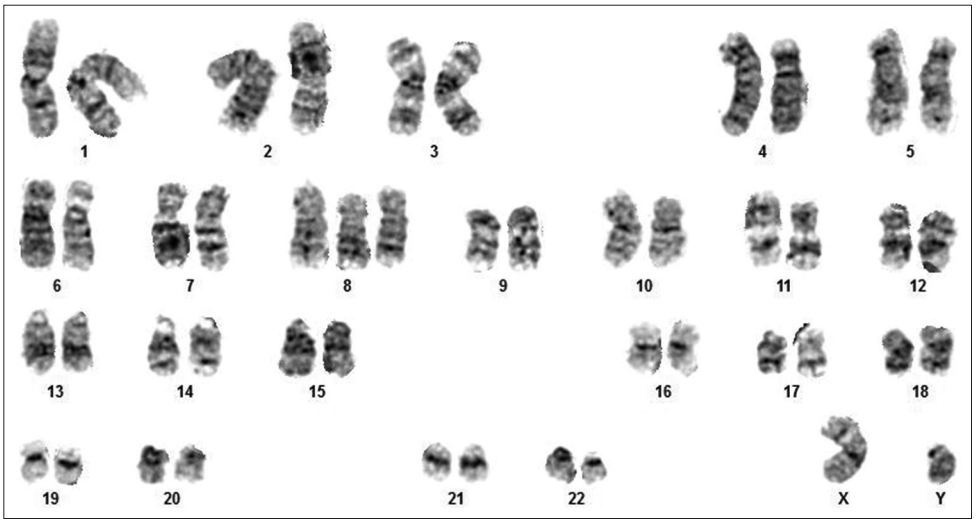

Figure 3: Cytogenetic study. Trisomy 8 without typical t(15;17)

and potentially even superior, to ATRA and idarubicin. The 2-year event-free survival rate was 97% in the ATRA–ATO group, compared to 86% in the ATRA–chemotherapy group.[16] Given the superior outcomes demonstrated in the phase 3 trial, we used the ATRA plus ATO regimen for our patient.

Our patient also had a good response to standard APL therapy with ATRA plus ATO, and he achieved complete hematologic and molecular remission during consolidation. This outcome is compatible with previous data suggesting that cryptic APL cases, despite their additional chromosomal abnormality, respond similarly to conventional APL treatment regimens.

In conclusion, diagnosing cryptic APL remains challenging, especially in patients presenting with persistent pancytopenia, thrombocytopenia, and inconclusive initial workup. In such cases, FISH and RT-PCR play an important role in identifying the *PML::RARA* rearrangement, which may be missed by conventional methods. There is no difference in treatment between cryptic APL and typical APL. Our case demonstrates that patients with cryptic AML with additional chromosomal abnormalities can achieve a favorable treatment response to standard ATRA and ATO therapy.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contributions

Dr. Hsiang-Jung Huang was responsible for patient care, data collection, literature review, and drafting of the manuscript. Dr. Sheng-Chuan Huang contributed to data acquisition and interpretation of clinical findings. Dr. Fang-Yu Wang assisted with manuscript revision and provided intellectual input. Dr. Chi-Cheng Li supervised the study and critically reviewed the manuscript. All authors have read and agreed to the final version of the manuscript.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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