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Cytological Abnormalities and Diagnostic Challenges in Variant Acute Promyelocytic Leukemia (APLv): A PML–RARA–Negative Case

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Abstract **Case Report**

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia usually associated with the t(15;17) (q24 ; q21) translocation and the PML-RARA fusion gene. Rare variant forms lacking this rearrangement may evade conventional cytogenetic detection, present with atypical morphology, and pose significant diagnostic and therapeutic challenges despite the hematologic emergency nature of APL. We report a 67-year-old man admitted for fever, weight loss, and severe bilateral epistaxis. Laboratory evaluation revealed anemia, marked hyperleukocytosis, and coagulation abnormalities consistent with disseminated intravascular coagulation. Peripheral blood smear showed 92% hypogranular blasts with occasional bilobed nuclei and rare Auer rods; myeloperoxidase cytochemistry demonstrated characteristic bundles. Immunophenotyping confirmed a myeloid phenotype with absence of CD34 and HLA-DR expression. Conventional karyotyping and fluorescence in situ hybridization were normal, whereas next-generation sequencing identified FLT3, IDH1, and NRAS mutations without evidence of PML-RARA fusion. Initial treatment with all-trans retinoic acid and corticosteroids was followed by azacitidine and venetoclax due to lack of response. This case underscores the diagnostic complexity of PML-RARA-negative APL-like presentations and highlights the essential role of advanced molecular techniques in guiding appropriate therapeutic decisions.

Keywords: Acute Promyelocytic Leukemia, PML-RARA fusion, Hypogranular variant, Disseminated Intravascular Coagulation, Immunophenotyping, Next-generation sequencing.

INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct entity within acute myeloid leukemias (AML), defined by the clonal accumulation of promyelocytes and the t(15;17)(q24;q21) translocation generating the PML–RARA fusion gene. It accounts for approximately 10–15% of AML cases, occurs predominantly in middle-aged adults, and frequently presents with severe hemorrhagic complications related to disseminated intravascular coagulation (DIC) [1].

In approximately 2% of cases, the classical translocation is not detectable by conventional karyotyping, corresponding to atypical forms. These include simple, complex, or cryptic variants, in which only molecular techniques (PCR or FISH) allow identification of the PML–RARA fusion [2].

Morphologically, two main subtypes are recognized: the hypergranular (classical) form and the hypogranular (or microgranular) form. The latter, referred to as variant APL (APLv), accounts for 15–20% of cases, is often associated with marked hyperleukocytosis, and is characterized by bilobed or multilobed nuclei with sparse granulation. A hyperbasophilic form remains exceptional [3–4]. Immunophenotyping typically demonstrates absence of CD34 and HLA-DR expression, along with low side scatter, which facilitates diagnostic orientation [5].

Rapid identification of APL relies on the integration of morphological, immunophenotypic, and molecular criteria (FISH or PCR) [6]. However, certain atypical presentations may mimic other AML subtypes (M1, M2, M4), making the initial diagnosis challenging [7]. In this context, we report a case of variant APL with

atypical morphology illustrating these diagnostic difficulties.

CASE REPORT

In June 2025, a 67-year-old man, a retired former military serviceman and chronic smoker, with no significant past medical history, was admitted for a one-month history of progressive deterioration of general condition, characterized by asthenia, anorexia, and an 8-kg weight loss. This was associated with a febrile episode reaching 39.9 °C without an identifiable infectious focus and was complicated at admission by severe epistaxis. Physical examination revealed mucocutaneous pallor, blood pressure of 106/71 mmHg, heart rate of 96 beats per minute, and oxygen saturation of 94% on room air. There was no evidence of tumor syndrome, with no palpable masses, hepatomegaly, splenomegaly, or gingival hypertrophy.

Complete blood count showed marked hyperleukocytosis at 132,300/mm³, with neutrophils 3,099/mm³, lymphocytes 47,518/mm³, monocytes 69,059/mm³, and thrombocytopenia at 48,000/mm³. Anemia was present (hemoglobin 8.9 g/dL), with a mean corpuscular volume of 98.5 fL, mean corpuscular hemoglobin concentration of 33.3 g/dL, and reticulocyte count of 19 G/L.

Peripheral blood smear stained with May–Grünwald–Giemsa was infiltrated by 92% blasts. Some blasts exhibited bilobed "butterfly-shaped" nuclei, with Auer rods identified in a few cells at the limit of MGG staining. Myeloperoxidase cytochemistry was strongly positive (93%), revealing the unexpected presence of multiple Auer rod bundles in several cells (Figure 1). Coagulation studies were abnormal, with a prothrombin time of 53%, fibrinogen level of 2.6 g/L, D-dimer concentration of 3 µg/mL, and an activated partial thromboplastin time ratio of 2.3, suggesting disseminated intravascular coagulation. Creatinine clearance was estimated at 89 mL/min/1.73 m² using the MDRD formula. Liver function tests were within normal limits except for mildly elevated AST at 66 U/L (normal < 35 U/L). Lactate dehydrogenase levels were increased to 621 U/L. Vitamin B12 was elevated at 1,122 pg/mL (normal range 187–883 pg/mL), while folate levels were within normal range at 6.70 ng/mL (normal range 3.1–20 ng/mL).

Initially, AML subtypes M2 or M4 were considered. However, the presence of Auer rod bundles in some blasts, together with their prominent visualization on MPO staining, supported the diagnosis of AML M3 (APL). Bone marrow aspiration demonstrated marrow infiltration exceeding 80% by blasts similar to those observed in peripheral blood, characterized by hypogranular cytoplasm and butterfly-shaped nuclei on MGG staining (Figure 2).

Flow cytometric analysis performed on bone marrow aspirate showed 93% immature cells with high forward scatter, confirming acute myeloid leukemia with the following immunophenotype: $CD33^+$, $CD117^+$, $CD13^+$, MPO^+, $CD4^+$, with absence of CD34 and HLA-DR expression, and no lymphoid markers.

Conventional cytogenetic analysis revealed no clonal chromosomal abnormalities in the metaphases analyzed. FISH analysis confirmed the absence of rearrangement, gain, or loss of the *KMT2A* (11q23) locus, as well as the absence of *PML–RARA* rearrangement or t(15;17)(q24;q21) translocation in all cells examined. Next-generation sequencing identified hotspot mutations in *NPM1*, *FLT3* (TKD), *IDH1*, and *NRAS*, with absence of the *PML–RARA* fusion gene.

Given the strong suspicion of acute promyelocytic leukemia, corticosteroid therapy and ATRA were initiated as first-line treatment but without clinical improvement. Treatment was subsequently redirected toward chemotherapy. The patient is currently undergoing induction therapy with two cycles of azacitidine (VIDAZA®). Clinically, the hemorrhagic syndrome resolved, and the patient achieved complete remission 36 days after admission, with a white blood cell count of 6.7 G/µL, hemoglobin level of 12 g/dL, and platelet count of 254 G/µL. Follow-up peripheral blood smear showed no circulating blasts. The reevaluation bone marrow aspirate was unfortunately diluted and did not allow confirmation of marrow morphology.

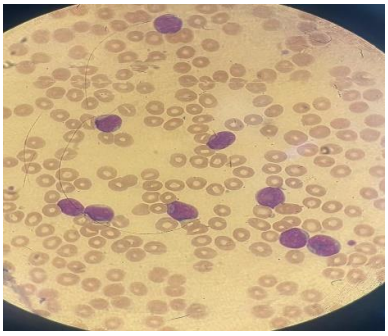

Figure 1: Peripheral blood smear (May–Grünwald–Giemsa stain, ×1000) showing circulating blasts with pale, frequently hypogranular cytoplasm

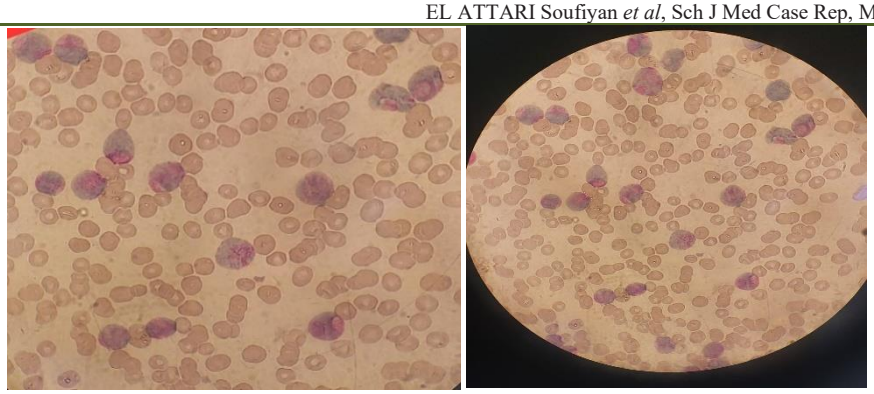

Figure 2: Cytochemical myeloperoxidase staining (×1000) demonstrating bundles of Auer rods in several blasts

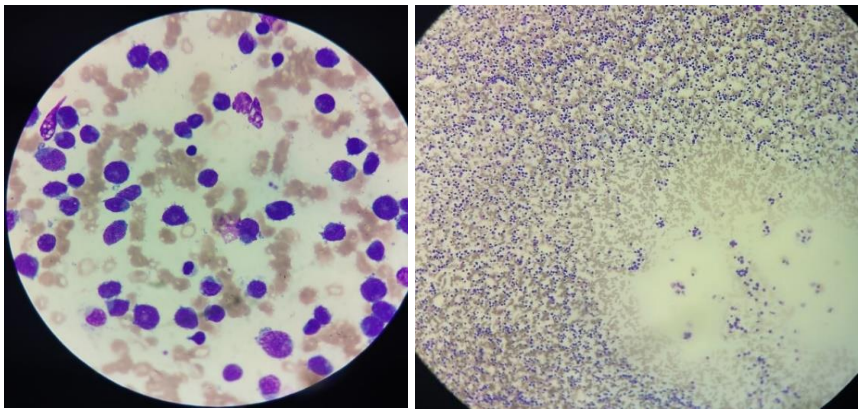

Figure 3: 3a. Bone marrow smear at low magnification (May–Grünwald–Giemsa stain, ×100) showing a rich, hypercellular marrow. 3b. Hypogranular blast without visible Auer rods (May–Grünwald–Giemsa stain, ×1000)

DISCUSSION

Acute promyelocytic leukemia (APL, or AML M3) represents a major hematological emergency due to its often rapidly fatal natural course, primarily related to severe hemorrhagic complications secondary to disseminated intravascular coagulation (DIC). Nevertheless, prognosis has been dramatically improved when an early diagnosis is established and prompte initiation of specific therapy based on all-trans retinoic acid (ATRA) and/or arsenic is achieved. In this context, initial morphological recognition of leukemic cells is a critical step, particularly since APL is one of the few acute leukemias in which targeted therapy can transform a life-threatening emergency into a highly curable disease.

Morphologically, the classical form of APL is characterized by abnormal hypergranular promyelocytes, frequently associated with bundles of Auer rods, sometimes occurring in a setting of peripheral leukopenia that may delay diagnostic suspicion. From a cytogenetic standpoint, the balanced translocation t(15;17) (q24;q21), resulting in the *PML–RARA* fusion gene, represents the pathognomonic molecular hallmark of the disease [9,10]. However, approximately 15–20% of cases correspond to the microgranular variant, whose morphological presentation (basophilic cytoplasm, sparse granulation, leukocytosis) differs markedly and is associated with a generally less favorable prognosis [11]. Even more rarely, atypical morphologies have been reported, accounting for 0.80–1.08% of cases [12].

Our observation clearly illustrates these diagnostic challenges. Most blast cells did not display the typical appearance of hypergranular promyelocytes, initially suggesting AML subtypes M2 or M4. Nevertheless, more subtle morphological features—such as bilobed “butterfly-shaped” nuclei, isolated Auer rods, and strong myeloperoxidase positivity—redirected the diagnostic hypothesis toward a promyelocytic component. This scenario underscores the critical importance of morphological expertise in atypical cases, in which the initial presentation may be misleading.

From a genetic perspective, the situation becomes even more complex. Approximately 2% of APL cases exhibit atypical cytogenetic rearrangements involving fusion partners other than *PML* [13]. These cytogenetic variants are classified into three categories: (I) simple variants, involving an additional chromosome rather than a direct exchange between chromosomes 15 and 17; (II) complex variants, involving at least three chromosomes including the *PML* and *RARA* loci; and (III) cryptic variants, in which morphology and cellular phenotype are suggestive of APL [2]. These abnormalities may escape conventional karyotyping and are detectable only by specific molecular biology techniques [14]. In our case, immunophenotyping supported a myeloid origin with a promyelocytic

component, whereas karyotype, FISH, and PCR analyses remained strictly normal. This discordant profile is characteristic of so-called "cryptic" forms, in which the *PML–RARA* translocation is undetectable using standard methods [15,16]. This highlights the technical limitations of conventional cytogenetic tools, whose resolution remains insufficient to identify certain rare rearrangements.

Therapeutic management is highly dependent on accurate identification of these molecular alterations. While in high-risk classical APL the combination of ATRA, arsenic trioxide (ATO), and chemotherapy significantly improves outcomes, variant forms continue to pose major challenges in both diagnosis and therapeutic strategy [13]. Certain fusions involving *RARA* and rare partners (such as *ZBTB16/PLZF*, *NUMA1*, *NPM1*, *STAT5B*, among others) are associated with suboptimal response to ATRA and ATO, or even partial therapeutic resistance [17]. In such situations, conventional chemotherapy often becomes the cornerstone of treatment, in contrast to the management of classical APL [18]. Rapid distinction between typical and variant forms therefore represents a major clinical issue, as it directly influences therapeutic choices and may affect long-term prognosis.

Since the identification of the *PML–RARA* fusion, it has become well established that its absence does not exclude the morphological diagnosis of APL. Multicenter studies, such as the British UK MRC ATRA trial, have demonstrated that only 87% of patients with molecular evidence of *PML–RARA* fusion had a detectable t(15;17) by conventional cytogenetics. Among the remaining cases, approximately 2% were attributed to cryptic rearrangements [19]. In this context, morphological evaluation, cytochemistry, and flow cytometry remain essential tools for rapidly initiating appropriate therapeutic management [20].

In our case, the therapeutic response was insufficient, consistent with data from the literature regarding certain variant forms. Although some cryptic fusions may respond favorably to conventional treatments [21], others exhibit significant chemoresistance. This emphasizes the crucial importance of comprehensive molecular characterization to optimally tailor therapeutic strategies for each patient. Systematic integration of high-sensitivity molecular techniques could therefore improve diagnostic accuracy, guide clinical decision-making, and ultimately optimize the prognosis of atypical forms of APL.

CONCLUSION

This case highlights several key points. First, atypical morphology may obscure the diagnosis of variant APL, making the early integration of morphological, immunophenotypic, and clinical data essential. Second, normal karyotype and FISH results do not exclude APL, particularly in cryptic or variant forms, and the use of high-sensitivity molecular techniques (NGS, RT-PCR) is crucial to facilitate diagnosis and accurately identify the underlying rearrangement. Finally, certain variant forms are associated with reduced therapeutic response, underscoring the need for increased vigilance in patient monitoring and individualized treatment strategies.

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