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– CASE REPORT –

The Overture of DIC: An APL Case from Community to Cure

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Abstract

Introduction: *Acute promyelocytic leukemia (APL; M3) is a distinct subtype of acute myeloid leukemia characterized by fusion of the promyelocytic leukemia (PML) gene with retinoic acid receptor alpha (RARA), most often resulting from the t(15;17)(q24;q21) translocation. APL is uniquely associated with disseminated intravascular coagulation and life-threatening bleeding, making it a hematologic emergency. Despite excellent long-term outcomes with all-trans retinoic acid–based therapy, early mortality remains significant, particularly when diagnosis or treatment is delayed.*

Case Presentation: *A 59-year-old man with multiple comorbidities presented with gastrointestinal bleeding, hematuria, mucosal hemorrhage, and pancytopenia. Laboratory evaluation demonstrated overt disseminated intravascular coagulation with severe thrombocytopenia and hypofibrinogenemia. Peripheral blood smear and bone marrow examination revealed abnormal promyelocytes containing Auer rods. Cytogenetic and molecular analyses confirmed acute promyelocytic leukemia with t(15;17)(q24;q21) and an additional abnormality of trisomy 8. Owing to profound coagulopathy and high bleeding risk, the patient required aggressive transfusional support and was transferred to a tertiary leukemia center for definitive care.*

Conclusion: *This case emphasizes the importance of early recognition of APL in patients with unexplained bleeding and cytopenias. Rapid cytogenetic confirmation and immediate initiation of ATRA are essential to reduce early mortality. Standardized referral pathways are essential to improve outcomes and reduce deaths.*

Keywords: *Acute promyelocytic leukemia (APL); PML–RARA fusion; t(15;17)(q24;q21); Trisomy 8; Disseminated intravascular coagulation (DIC); Pancytopenia; Gastrointestinal/mucosal bleeding; Early diagnosis; Cytogenetic testing.*

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Introduction

Acute promyelocytic leukemia (APL) is a unique and aggressive form of acute myeloid leukemia (AML) that constitutes about 10–15% of all AML cases in adults[1]. It is characterized by the balanced reciprocal translocation t(15;17)(q24;q21), which results in the fusion of the promyelocytic leukemia (PML) and retinoic acid receptor alpha (RARA) genes[2]. The resulting fusion protein inhibits myeloid differentiation and promotes a

hyperfibrinolytic and prothrombotic state, presenting clinically as disseminated intravascular coagulation (DIC)[3]. To illustrate this, **Figure 1** provides a schematic overview of the diagnostic pathway, highlighting the interplay between clinical suspicion, hematologic evaluation, and confirmatory testing.

Before the development of targeted therapies, APL had the highest early mortality of all AML subtypes, with most patients dying from catastrophic central nervous system or gastrointestinal bleeding within days of presentation[4].

The discovery of all-trans retinoic acid (ATRA) in the late 1980s, followed by arsenic trioxide (ATO), redefined APL from a highly fatal leukemia to one of the most treatable hematologic malignancies, with survival in contemporary cohorts exceeds 80–90% [5,6]. **Figure 1** schematically outlines the diagnostic pathway in suspected APL, emphasizing the sequence from clinical suspicion and laboratory abnormalities to morphologic and molecular confirmation.

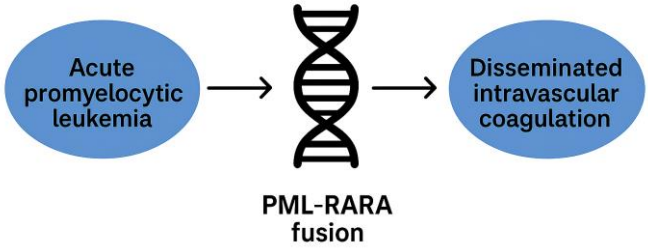

Figure 1. *Summary of the diagnostic pathway in APL, marking the points of clinical suspicion, laboratory abnormality, peripheral smear, bone marrow morphology, and molecular confirmation*

However, real-world results are heterogeneous. SEER database and European LeukemiaNet studies have revealed that early death were between 10-20% and was primarily the result of delays in diagnosis, delays in access to ATRA, or complications such as differentiation syndrome. Additional cytogenetic abnormalities, such as trisomy 8, are present in 10–15% of APL cases and raise questions about prognostic significance and/or the benefit of ATRA/ATO-based therapy [7,8,9].

This case highlights the significant discrepancy between evidence-based best practices and what actually occurs in practice when caring for patients with acute promyelocytic leukemia (APL). It shows that when clinicians evaluate patients for signs and symptoms of APL, the information they gather about a patient may be correct based on both laboratory testing results and physical examination (classical morphologic features), but significant obstacles remain at the systemic level that can result in delays during treatment and/or transfer of APL patients to more appropriate treatment facilities during a time of extreme risk of bleeding (e.g., early in the course of disease). This case emphasises the need for greater awareness of APL, early initiation of ATRA based solely on suspicion, and adequate preparedness of healthcare institutions for the management of APL, to prevent the premature death of patients with APL.

Case Presentation

A 59-year-old man with hypertension, diabetes mellitus, hyperlipidemia, and gastroesophageal reflux disease presented with 2 weeks of diarrhea and hematuria, bruising, and fatigue. He reported black, tarry stools, bright red clots in urine, recurrent blood blisters in the oral mucosa, and intermittent bleeding from the left ear. He denied experiencing fever, night sweats, or contact with individuals who were sick. Physical examination at admission, he was afebrile, hemodynamically stable, and fully alert. He was pale, mildly jaundiced, with scattered petechiae on his trunk and extremities and larger ecchymoses. His oral cavity exam noted the presence of hemorrhagic bullae. There was no evidence of hepatosplenomegaly or lymphadenopathy. **Figure 2** visually summarizes the key diagnostic features of this case, including peripheral smear abnormalities, bone marrow hypercellularity, and molecular confirmation of PML–RARA.

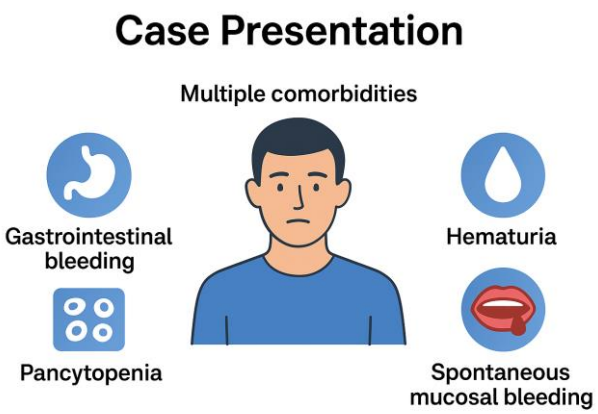

Figure 2. *Case-specific diagnostic highlights include a peripheral smear showing abnormal promyelocytes with Auer rods, bone marrow hypercellularity, and evidence of the PML-RARA fusion on molecular testing.*

Laboratory Findings CBC: Hemoglobin 10.2 g/dL; platelets 10 ×10⁹/L; WBC 0.91 ×10⁹/L (ANC 0.4 ×10⁹/L). Coagulation panel: Prolonged PT; increased INR; markedly elevated D-dimer; hypofibrinogenemia - consistent with overt DIC. CMP: Mild transaminitis; elevated LDH; stable creatinine.

Imaging CT Abdomen/Pelvis: Hepatic steatosis; stable complex right renal cyst; no active bleeding. Chest CT: Tiny nodule in the right middle lobe measuring 0.4 cm; mild bilateral fibrosis/atelectasis. Head CT: No evidence of an acute bleed; chronic mastoid changes.

Peripheral Smear & Bone Marrow: The peripheral smear revealed severe thrombocytopenia, occasional blasts, and promyelocytes with heavy granulation and Auer rods. The bone marrow biopsy demonstrated approximately 82% atypical promyelocytes with bilobed nuclei and frequent Auer rods. Cytogenetics: Karyotype: 47,XY,+8,der(15;17)(q24;q21)[20]/46,XY[1] FISH: Positive for PML-RARA fusion. Representative images from the peripheral smear, bone marrow biopsy, and FISH study are shown together in **Figure 3**. **Figure 3** demonstrates the morphologic and cytogenetic hallmarks supporting the diagnosis, including abnormal promyelocytes with Auer rods and confirmatory PML–RARA fusion by FISH.

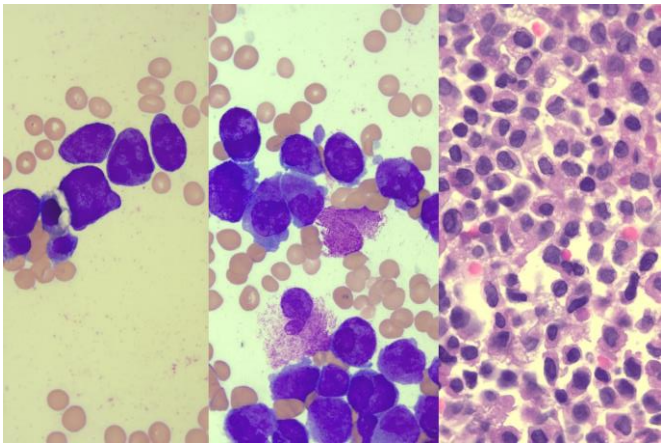

Figure 3. *Diagnostic findings characteristic of acute promyelocytic leukemia (APL). The composite figure illustrates: (A) Peripheral blood smear exhibiting severe thrombocytopenia, with rare circulating blasts, and abnormal promyelocytes with heavy granulation and Auer rods. (B) Bone marrow biopsy with approximately 82% atypical promyelocytes, many with bilobed nuclei and Auer rods. (C) FISH, confirming PML-RARA fusion. An additional cytogenetic finding of trisomy 8, which is known but not independently prognostic in APL.*

Additional finding: Trisomy 8. Hospital Course: Due to severe thrombocytopenia and evidence of coagulopathy, the patient was transfused with multiple platelet units to maintain platelet counts above 30 x 10^9/L, cryoprecipitate to maintain fibrinogen concentration above 150 mg/dL, and red blood cells to maintain hemoglobin concentration above 8 g/dL. The patient was also placed on broad-spectrum antibiotics due to evidence of neutropenia. Although the patient experienced gastrointestinal bleeding requiring endoscopy for evaluation, this could not be performed due to the risk of extreme hemorrhage.

Hematology-oncology was consulted urgently to evaluate the patient. Given the very significant concern for APL, plans were also initiated to transfer the patient to a tertiary care leukemia center, where ATRA and ATO-based induction therapy could be rapidly initiated. A summary of the key laboratory and diagnostic findings is provided in **Table 1**.

Table 1. *Key Laboratory and Diagnostic Findings in the Patient with APL*

Parameter	Finding	Reference/Comment
Hemoglobin	10.2 g/dL	Anemia
Platelets	10 ×10⁹/L	Severe thrombocytopenia
WBC	0.91 ×10⁹/L (ANC 0.4 ×10⁹/L)	Neutropenia
PT/INR	Prolonged / Elevated	Consistent with DIC
Fibrinogen	Low	DIC
D-dimer	Markedly elevated	Hyperfibrinolysis
Peripheral smear	Promyelocytes with Auer rods	Classical APL morphology
Bone marrow	82% atypical promyelocytes	Hypercellular
Cytogenetics	t(15;17), +8	PML-RARA fusion, trisomy 8
FISH	PML-RARA positive	Confirms APL

Discussion

This case illustrates the typical yet potentially fatal presentation of APL: mucocutaneous bleeding, hematuria, and gastrointestinal bleeding in the context of laboratory-documented disseminated intravascular coagulation (DIC). Early bleeding deaths continue to be the most significant early hazard in APL, and rapid identification and aggressive supportive care are the best approaches to decreasing early deaths [3,6]. The presence of Auer rods on smear and hypercellular bone marrow with promyelocytes strongly suggests APL, and molecular confirmation by PML-RARA fusion in the peripheral blood or bone marrow establishes the diagnosis and directs definitive therapy.

Pathophysiology and Clinical Features

APL is distinct from other types of acute myeloid leukemia due to its strong association with life-threatening coagulopathy. Leukemic promyelocytes express tissue factor and a cancer procoagulant, leading to a consumptive DIC picture, coupled with secondary hyperfibrinolysis [3,10]. These pathophysiologic explanations account for the common clinical manifestations of mucocutaneous, intracranial, and gastrointestinal bleeding observed in our patient.

Challenges of diagnosis by Community Hospitals

The high early mortality rate associated with APL is mainly due to delays in diagnosis and initiation of therapy[7]. Conversely, community hospitals face barriers, including concerns about having immediate access to ATRA, not wanting to initiate therapy without cytogenetic confirmation, and limited support for transfusions. Nonetheless, guidelines recommend empiric ATRA initiation as soon as APL is suspected, before confirmation by FISH or PCR[5,11]. Our case demonstrates the need for awareness and protocols in community settings to close this critical gap.

Cytogenetic Abnormalities

The cytogenetic feature most characteristic of APL is the balanced reciprocal translocation t (15;17), which results in the fusion of the promyelocytic leukemia (PML) and retinoic acid receptor alpha (RARA) genes[2]. Other changes are detected in about 30–40% of patients, and the accompanying cytogenetic abnormality is most commonly trisomy 8[9]. While such findings raise the

prospect of clonal complexity, their prognostic impact is negligible when patients are treated with ATRA and arsenic trioxide (ATO). In fact, some reports suggest that mutations may be associated with the risk of relapse for high-risk patients, thereby requiring closer follow-up [12].

Challenges of diagnosis by Community Hospitals

The high incidence of early mortality related to APL is primarily attributed to the lag in diagnosing and starting definitive therapy, most notably all-trans retinoic acid (ATRA), for patients with APL. While most tertiary leukemia centers have guidelines and immediate access to ATRA, several obstacles prevent community hospitals from having similar access or from making treatment decisions in the real world[13]. These obstacles include the lack of ATRA at the community hospital, reluctance to provide empiric treatment for APL without cytogenetic confirmation, competing acute medical priorities for patients at the community hospital, and logistical issues with obtaining transfusion support and arranging prompt transfer[14].

As demonstrated in this case, despite strong morphologic suspicion of APL, as indicated by the peripheral blood smear and laboratory findings consistent with DIC, the patient was unable to receive definitive induction therapy at the local hospital due to system-related limitations and was transferred to a tertiary medical center, resulting in an unavoidable delay during this period of substantial hemorrhagic risk. Current recommendations from international guidelines supporting empiric treatment with ATRA should be initiated when APL is suspected to reduce the likelihood of early mortality compared with waiting for molecular documentation (e.g., FISH/PCR), and to weigh the benefits against the potential risk of overtreatment[15].

Thus, this case illustrates a significant disparity between guidelines and their implementation and acceptability in the community setting. To minimize avoidable premature deaths, standardization of the protocols developed by the facility, a regional strategy for drug stocking, and prompt involvement of hematologists are necessary.

Molecular Diagnostics and Health-System Implications

In addition to morphology and cytogenetics, modern oncology practice is increasingly utilizing minimally invasive molecular techniques to facilitate treatment decision-making. Among solid tumors, plasma-based genotyping has been demonstrated to reduce time to an appropriate targeted therapy and increase the availability of personalized treatment[16]. Liquid biopsy and circulating nucleic acid testing are now supported by international consensus statements that recommend standardized workflows and clinical indications[17]. These recommendations highlight the broader context of transitioning to rapid molecular diagnostics and could serve as a framework for acute hematologic emergencies of APL. The evolving context of biomarker-driven oncology also underscores the need for fast access to targeted agents. Reviews have noted that outcomes are better with proactive, biomarker-forward approaches that use streamlined diagnosis and therapy[18]. In APL, this translates to initiating empiric ATRA at the first suspicion, maintaining transfusion readiness, and ensuring that life-saving agents are stocked regionally to prevent transfer and delay. **Figure 4** highlights these therapeutic principles, compares the standard treatment pathway with the unique considerations that emerged in this case, and summarizes the clinical decision-making framework applied in practice.

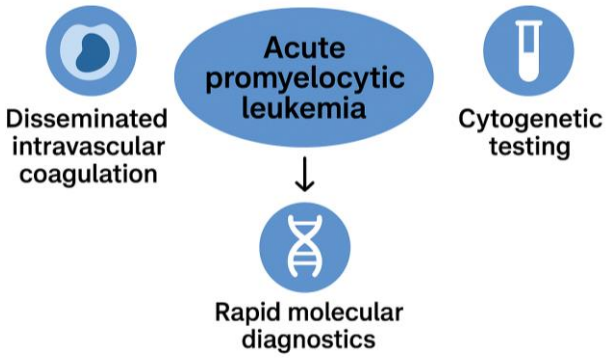

Figure 4. *Schematic summary of therapeutic principles in APL, which underscore the urgent initiation of ATRA-based therapy, supportive infusions, and directional thinking to consider in managing this case.*

Confirmatory testing being required before starting treatment is a suitable clinical strategy; however, in situations where molecular testing is delayed or not available, this strategy may paradoxically result in increased early mortality from leukemia. This case demonstrates the need for parallel rather than sequential diagnostic and treatment approaches—where patients receive both immediate initiation of ATRA and transfusion support while molecular testing is occurring[19]. For health systems to effectively bring the benefits seen in clinical trials to patients with leukemia in the community, they must create proactive, biomarker-driven models of care that provide rapid access to ATRA, rapid molecular testing protocols, and a clearly defined plan for advancing care based on molecular test results[20].

Comparative Literature

Population-based SEER studies reveal that approximately 17% of patients with APL die early due primarily to bleeding. European studies indicate that ready access to ATRA significantly reduces this risk, highlighting disparities in access to system-level factors. Case series support the notion that while trisomy 8 is common, it does not independently prognosticate unfavorable outcomes in the era of ATRA/ATO [21].

This case illustrates the importance of:
1. Timeliness of ATRA initiation — empiric treatment should not be withheld when clinical suspicion for APL is high, even in the presence of atypical features or pending cytogenetic confirmation.
2. Early recognition and escalation — frontline clinicians must recognize the constellation of pancytopenia, abnormal promyelocytes, and DIC as a hematologic emergency.
3. Institutional preparedness — community hospitals should maintain access to ATRA or formalized rapid-transfer protocols to prevent treatment delays.
4. System-level readiness — predefined transfusion algorithms and rapid molecular workflows are critical to reducing early hemorrhagic mortality.

Conclusion

APL remains a hematologic emergency, even with significant advances in therapeutic options. There is a pattern of early recognition of this disease - pancytopenia, abnormal promyelocytes, and bleeding with laboratory DIC - that should prompt the initiation of empiric ATRA even before testing is obtained. This case illustrates the classic findings and demonstrates the improvements in care for patients with APL, as well as the ongoing challenges in translating trial-level success into real-world outcomes.

Declarations
Conflict of Interest: The authors declare no conflicts of interest.
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Informed Consent: Written informed consent for publication of this case and accompanying images was obtained from the patient.
Authors' Contributions: NS drafted the manuscript; VAG contributed pathology interpretation; KZ provided hematology-oncology expertise and critical revision. All authors approved the final manuscript.
Data Availability: Data sharing does not apply to this case report.

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