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BRIEF REPORT

Dual Thrombotic Complications in Acute Promyelocytic Leukemia: A Case of Cerebral Venous Thrombosis and Pulmonary Embolism

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Abstract

Introduction Acute promyelocytic leukemia (APML) is a distinct subtype of acute myeloid leukemia typically characterized by hemorrhagic complications due to coagulopathy. Thrombotic events as the initial presentation of APML are exceedingly rare. We report a rare case in which cerebral venous thrombosis (CVT) and pulmonary thromboembolism (PTE) were the initial manifestations of APML, highlighting an atypical clinical presentation and its successful management.

Clinical Presentation

A 35-year-old woman presented with a 1-month history of persistent headache and neck pain, followed by two weeks of hemoptysis, low-grade fever, fatigue, and anorexia. Laboratory investigations revealed leukopenia and circulating promyelocytes, with bone marrow aspiration showing > 80% promyelocytes with Auer rods (confirmed by PML/RARA FISH positivity), contrast-enhanced chest CT revealing PTE in the right pulmonary artery/inferior vena cava with right lower lobe infarction, and brain MRI/MRV demonstrating acute-subacute CVT with chronic left transverse sinus thrombosis.

She was diagnosed with low-risk APML complicated by PTE and CVT. Therapeutic management included anticoagulation (heparin bridged to warfarin) combined with ATRA and arsenic trioxide (ATO) induction therapy. This approach resulted in marked clinical and hematologic improvement, allowing for discharge with plans for consolidation therapy and outpatient follow-up, demonstrating the feasibility and efficacy of combined anticoagulation and APML-targeted therapy.

Conclusion This case highlights three crucial lessons: (1) APML can present with thrombotic complications before typical hemorrhagic manifestations or diagnosis, requiring heightened clinical suspicion; (2) concurrent management of thrombosis and APML with anticoagulation plus ATRA/ATO is both feasible and effective; and (3) multidisciplinary collaboration is essential for optimal outcomes in such complex presentations, emphasizing the need to consider APML in the differential diagnosis of unexplained thrombotic events.

Keywords Acute promyelocytic leukemia · Pulmonary thromboembolism · Cerebral sinus venous thrombosis (CVT)

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Introduction

Acute promyelocytic leukemia (APML) is a distinct subtype of acute myeloid leukemia (AML) defined by the t(15;17)(q24;q21) translocation, resulting in the PML/RARα fusion gene. This genetic alteration disrupts myeloid differentiation and underlies APML's unique coagulopathy, which manifests as severe bleeding complications, the leading cause of early mortality and paradoxical thrombotic events [1–4]. Thrombosis occurs in 2–15% of APML cases, exceeding rates observed in other leukemias, with venous thromboembolism including deep veins, the cerebral venous sinus, and the portal and hepatic veins. In contrast, arterial clots are most commonly associated with peripheral artery occlusion, myocardial infarction, and stroke, contributing to morbidity [4–7].

Cerebral venous sinus thrombosis (CVT), a rare but life-threatening thrombotic complication (0.5% of all strokes), is seldom reported as an initial presentation preceding APL diagnosis [4–7].

This case report describes a 35-year-old Ethiopian woman who presented with CVT and pulmonary thromboembolism (PTE) prior to APML recognition, highlighting the diagnostic challenges and clinical significance of coagulopathy in APML and integrated management of thrombosis and leukemia, particularly in resource-limited settings where diagnostic delays may exacerbate outcomes.

Case Presentation

A 35-year-old Ethiopian woman was referred to our tertiary care hematology center (day 0) for evaluation and management of suspected acute promyelocytic leukemia (APML) complicated by cerebral and pulmonary thromboses. Her symptoms began approximately 1 month prior (day −30) with persistent, severe global headache and neck pain. Around day −16, she developed a productive cough with hemoptysis, low-grade fever, progressive fatigue, anorexia, and unintentional weight loss. On day −11, she experienced a brief episode of vaginal bleeding, which was managed at a private hospital with a 3-day course of a combined oral contraceptive pill (ethinylestradiol). She reported no prior medical conditions or known family history of thrombotic disorders or hematologic malignancies. No genetic testing was conducted among family members to assess for inherited thrombophilia.

Initial Presentation and Referral (Day −11 to Day 0)

She was admitted at a private hospital where she was treated empirically for community-acquired pneumonia (CAP) with intravenous antibiotics. Persistent headache prompted brain MRI/MRV, which revealed cerebral venous thrombosis (CVT) involving the superior sagittal and left transverse sinuses (Fig. 1). A peripheral blood smear at this facility demonstrated leukopenia and circulating abnormal promyelocytes with Auer rods, strongly suggesting acute promyelocytic leukemia (APML). Due to this complex presentation of suspected hematologic malignancy with major thrombosis, she was transferred to our tertiary center for definitive diagnosis and management.

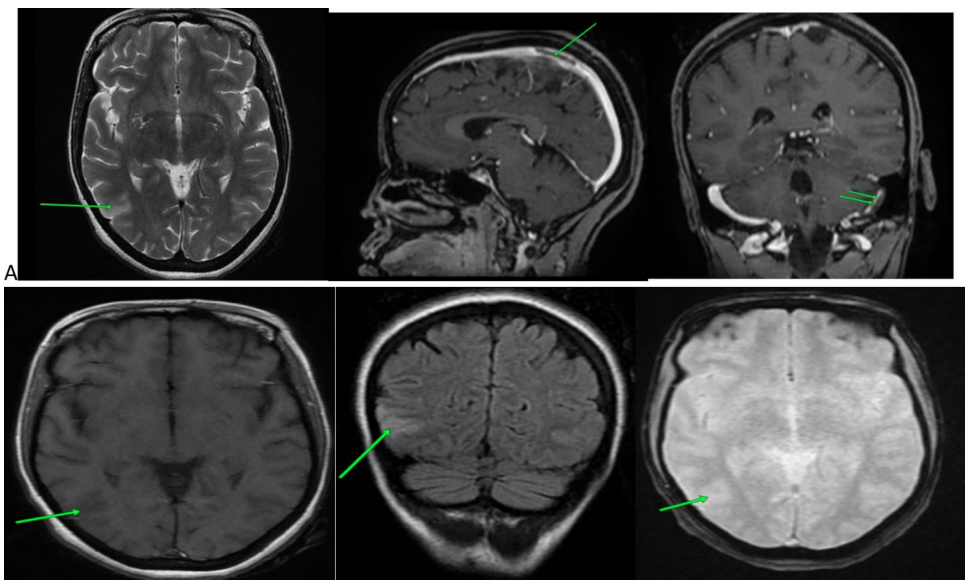

Fig. 1 Image **A**, **B**, **C**, **D**, **E**, **F**.: There is a partial filling defect over the superior sagittal sinus and left transverse sinus. There is also a right temporo-occipital cortical T1 hypo-, T2-, and FLAIR hyperintense signal, which has restrictions on DWI, with no blooming foci on SWI. The lesion has no enhancement on postcontrast imaging. No leptomeningeal enhancement was noted. This was consistent with SSS and left transverse sinus partial thrombosis with a venous infarction

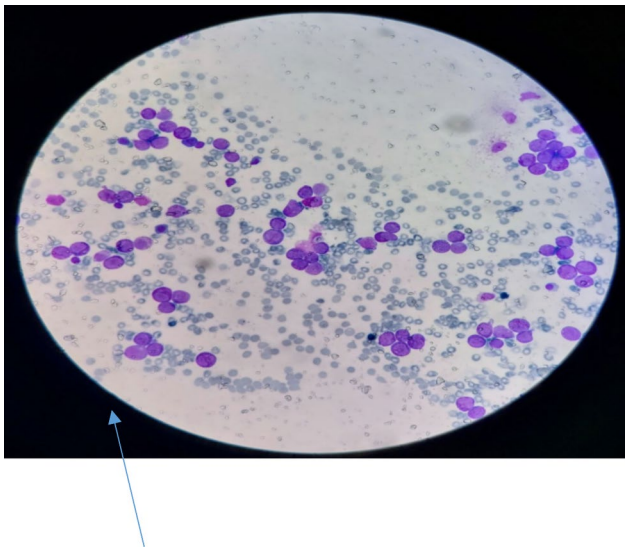

Fig. 2 Peripheral morphology; leukopenia with occasional promyelocytes (arrow)

Evaluation at Tertiary Center (Day 0 Onward)

On arrival, the patient was pale and tachycardic (HR 118 bpm), with BP 100/60 mmHg, RR 24 breaths/min, and oxygen saturation 85–87% on room air. She was afebrile. Lung auscultation revealed coarse crackles in the right lower lung field. Neurologically, she was alert and oriented without focal deficits. There was no lymphadenopathy or hepatosplenomegaly.

Laboratory tests showed leukopenia (WBC 3,400/µL), anemia (Hb 9.2 g/dL), thrombocytopenia (platelets 60,000/µL), and elevated LDH (252 U/L). HIV, HBV, and VDRL testing were negative. Peripheral smear confirmed promyelocytes with Auer rods (Fig. 2). Bone marrow biopsy revealed hypercellular marrow with > 80% promyelocytes (Figs. 3 and 4), and FISH analysis confirmed the PML/RARA fusion gene, establishing the diagnosis of APML.

Chest CT scan revealed pulmonary thromboembolism (PTE) involving the right pulmonary artery and inferior vena cava (IVC), with right lower lobe pulmonary) (Fig. 5). Pelvic ultrasound incidentally detected uterine fibroids. Autoimmune and antiphospholipid antibody panels were negative.

Diagnostic Challenges and Management

The diagnosis was delayed due to overlapping symptoms mimicking pneumonia and delayed expert hematopathology review. The thrombotic complications (CVT and PTE) masked typical bleeding signs of APML, contributing to diagnostic uncertainty. The strong suspicion of APML led to the initiation of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) therapy on day + 3, before molecular confirmation.

A multidisciplinary team including hematologists, neurologists, and radiologists managed the patient. Anticoagulation was started with intravenous heparin (aPTT goal 60–80 s), transitioned to warfarin (INR 2–3). Leukemia-directed therapy included ATRA (45 mg/m^2/day) and ATO (0.15 mg/kg/day). Supportive care included oxygen and blood transfusions. She was closely monitored for differentiation syndrome, which did not occur.

Outcome and Follow-Up

The patient's condition improved steadily, achieving complete hematologic remission. Repeat imaging showed partial resolution of thrombi. After 52 days of hospitalization, she was discharged on oral warfarin with therapeutic INR and continued outpatient follow-up. Bone marrow reassessment confirmed morphologic remission. She tolerated treatment well, with no major bleeding or differentiation syndrome. Mild headaches during ATRA initiation resolved without intervention.

Discussion

This case illustrates a rare and clinically challenging presentation of acute promyelocytic leukemia (APML), in which concurrent cerebral venous thrombosis (CVT) and pulmonary thromboembolism (PTE) were the initial manifestations. The successful use of ATRA and arsenic trioxide (ATO) alongside anticoagulation demonstrates the feasibility of managing high-risk thrombotic complications even

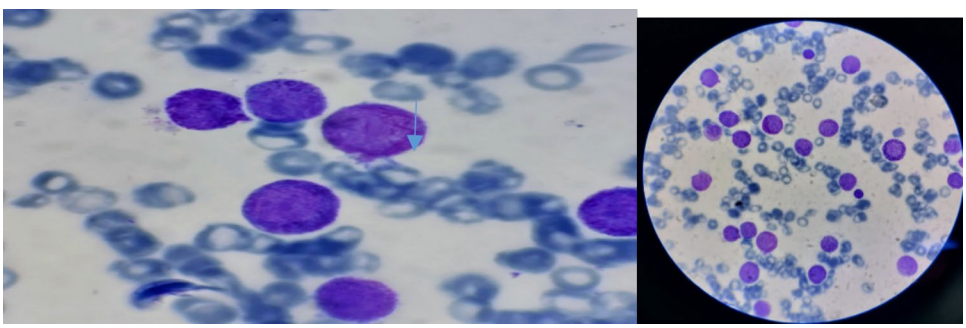

Fig. 3 Bone marrow aspirate: promyelocytes with coarse azurophilic granules and Auer Rods (arrow)

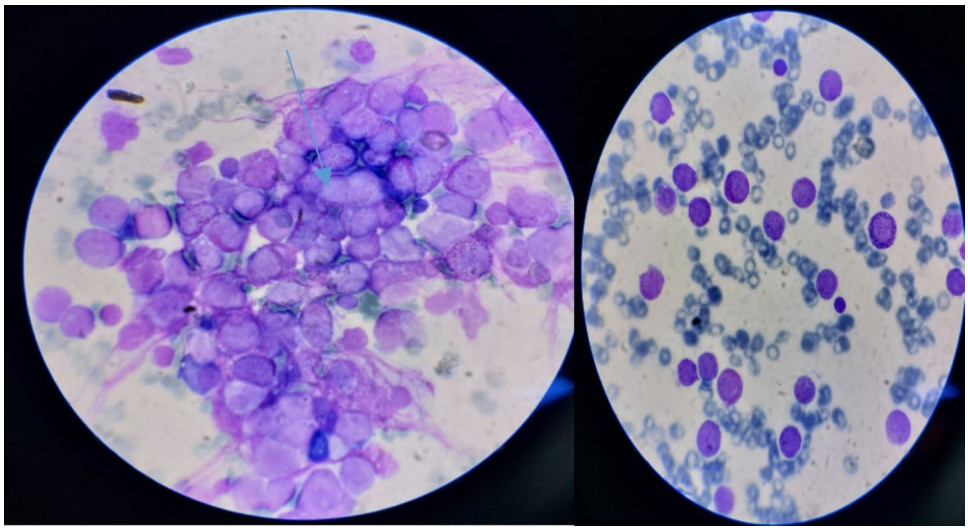

Fig. 4 Bone marrow aspirate: a cellular smear flooded with promyelocytes having coarse azurophilic granules

in resource-limited settings. This report provides valuable clinicopathological insight, supported by imaging-confirmed thrombosis and a comprehensive hematologic workup, while also drawing attention to demographic and geographic disparities in APL presentation—particularly among young African women.

APML is defined by the PML/RARA fusion gene and is characterized by a complex coagulopathy that predisposes to both hemorrhagic and thrombotic complications [1]. While bleeding is more frequently observed, thrombosis occurs in up to 20% of APL cases, particularly during the diagnostic or induction phases [2, 3, 5, 7–9]. The underlying mechanism involves leukemic expression of tissue factor (TF) and cancer procoagulant (CP), which activate the coagulation cascade and lead to excessive thrombin generation [10–12]. In parallel, proinflammatory cytokines such as IL-1β and TNFα contribute to endothelial injury and downregulation of natural anticoagulants like thrombomodulin, further exacerbating the prothrombotic state [13].

This patient's presentation with cerebral venous thrombosis (CVT) and pulmonary thromboembolism (PTE) aligns with reported thrombotic events in acute promyelocytic leukemia (APML). However, in contrast to many reported cases where additional risk factors such as oral contraceptive pill (OCP) use may contribute to thrombosis [14–17], the symptoms of CVT and PTE in this patient developed before she initiated OCPs. This suggests that the thrombotic events were primarily driven by the underlying APML-associated coagulopathy, rather than being triggered by exogenous hormonal exposure. CVT itself remains rare (1.3–2.6 cases per 100,000) but occurs more frequently in young females, often presenting with headaches in over 90% of cases [14–16, 18–22]. In African cohorts, CVT in APML also shows a marked female predominance—up to 80%—which is consistent with this Ethiopian case [18].

Therapeutically, ATRA/ATO achieves remission in > 90% of patients but may transiently worsen coagulopathy due to differentiation syndrome [3, 10, 23, 24]. Timely anticoagulation is supported by consensus guidelines even during cytopenia, though high-quality APML-specific trials remain lacking [10, 25]. This patient's management with heparin bridging to warfarin was successful, as reflected by full hematologic recovery at discharge (platelets: 406,000/μL).

The combination of APL-induced coagulopathy, OCP use, and endothelial injury from inflammatory cytokines likely culminated in this patient's CVT and PTE. APML drives a prothrombotic state through TF/CP activation and cytokine release, while OCPs further contribute to hypercoagulability, particularly in genetically or hormonally predisposed females [13–16]. The delayed presentation with subacute headache and hypoxia, although nonspecific, mirrors classical signs of CVT and pulmonary infarction. The patient's rapid hematologic and clinical improvement following ATRA/ATO induction and targeted anticoagulation further supports the reversibility of APML-associated thrombosis when treated early and appropriately.

Conclusions

This case highlights the critical need for early recognition and tailored management of thrombotic complications in acute promyelocytic leukemia. It underscores the importance of maintaining a high index of suspicion for CVT and pulmonary embolism in young females presenting with unexplained headaches or hypoxia, especially when hematologic abnormalities

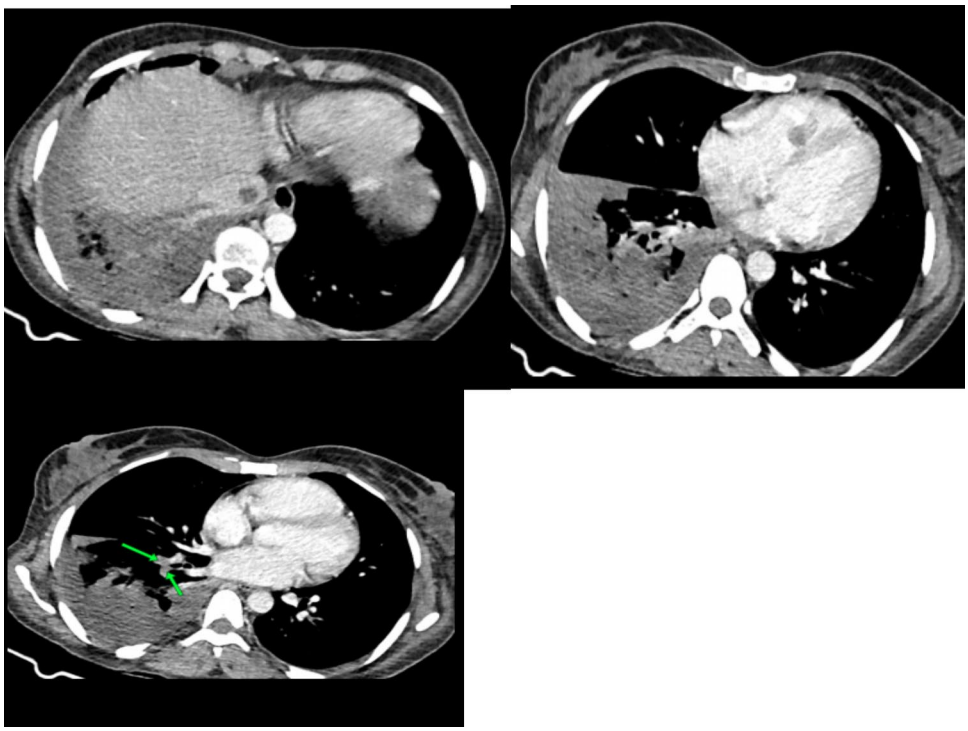

Fig. 5 Chest CT with contrast agent revealed a non-enhancing soft tissue filling defect over the IVC, right ventricle, and right inferior segmental and subsegmental pulmonary artery. There is also a right lower lobe peripherally located non-enhancing wedge-shaped opacity with adjacent pleural fluid collection, likely IVC, intracardiac, and right segmental pulmonary artery thrombosis with peripheral lung infarction

are present. The effective integration of APML-directed therapy and anticoagulation in a resource-limited setting reinforces that timely, evidence-based intervention can lead to favorable outcomes despite diagnostic and logistical challenges.

Patient Perspective

At first, I felt terrified and overwhelmed by my symptoms—the constant, severe headaches, extreme tiredness, and unexplained bleeding. After being transferred, I finally got the right diagnosis and treatment. The medications (ATRA and arsenic trioxide) and blood thinners helped me improve, and the doctors explained everything clearly. I'm grateful for the care I received and now feel hopeful about my recovery and future.

Abbreviations *ATO*: Arsenic trioxide; *AML*: Acute myeloid leukemia; *APML*: Acute promyelocytic leukemia; *ATRA*: All-trans retinoic acid; *BCR3*: Breakpoint cluster region 3 transcript; *CD*: Cluster of differentiation; *CP*: Cancer procoagulant; *CT scan*: Computed tomography scan; *CVT*: Cerebral sinus venous thrombosis; *DVT*: Deep vein thrombosis; *FISH*: Fluorescence in situ hybridization; *FLT3-ITD*: Fms-like tyrosine kinase 3 internal tandem duplication; *ICH*: Intracerebral hemorrhage; *INR*: International normalized ratio; *LDH*: Lactate dehydrogenase; *LMWH*: Low-molecular-weight heparin; *MRI*: Magnetic resonance imaging; *MRV*: Magnetic resonance venography; *OCPs*: Oral contraceptive pills; *PML/RARA*: Promyelocytic leukemia/retinoic acid receptor alpha fusion gene; *PTE*: Pulmonary thromboembolism; *TF*: Tissue factor; *UFH*: Unfractionated heparin; *WHO*: World Health Organization

Author Contributions Yadelew Jember Kassie; contributed to the conception of the report, data collection, and drafting of the manuscript. Temesgen Assefa Ayele; participated in patient management, literature review, and manuscript editing.Mustejib Abdla Hussen; was involved in literature review, interpretation of data, and revision of the manuscript for intellectual content.Yared Gebremicheal Tarekegn;assisted in data interpretation, reference organization, and formatting of the final version.Demamu Agegn Adugna; contributed to the radiological review and clinical data analysis.Bereket Bizuneh Bekele; assisted in case documentation, critical review, and final approval of the version to be submitted

Data Availability No datasets were generated or analysed during the current study.

Code Availability No custom code or software was used in the preparation or analysis of this case report.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Informed Consent The patient voluntarily provided written informed consent authorizing the publication of this case report and accompanying medical images. The signed consent documentation can be made available for review if required.

Consent for Publication Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing Interests The authors declare no competing interests.

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