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Deluging Thrombosis: An Unusual Presentation of Acute Promyelocytic Leukemia

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Abstract

Acute promyelocytic leukemia (APML) patients are prone to thrombosis. However, thrombosis at presentation is rare in APML. Our patient presented with thrombosis and cytopenia, and the clinical diagnosis was of paroxysmal nocturnal hemoglobinuria. However, subsequent peripheral blood smear and bone marrow study confirmed the diagnosis of APML. The patient was successfully managed with anticoagulation, arsenic trioxide, and all-trans retinoic acid.

Keywords: *Acute promyelocytic leukemia, anti-coagulation, chemotherapy, thrombosis*

Introduction

Acute promyelocytic leukemia (APML), a unique subtype of acute myeloid leukemia, is commonly associated with a complex life-threatening coagulopathy.[1] Induction therapy with all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) usually results in a durable remission. As compared to bleeding manifestations, APML-associated thrombotic events are less commonly reported.[2] They can occur either before, during, or after the induction therapy (40.4% prior to induction therapy) and exhibit predilection for both arterial (more common) and venous vasculature.[3,4] About half of these patients (51.6%) have coagulation defects.[4]

Case Report

A 20-year-old daily wage laborer was admitted with the complaints of the left lower limb swelling for a 2-week duration. Six weeks prior to admission, he was evaluated in a local hospital for low-grade fever and fatigue. Investigations done there had revealed anemia (Hb 72 g/L) and normal chest X-ray; peripheral smear was not examined. He was administered one unit of blood transfusion and discharged on oral haematinics. Six weeks later (now), he was referred to us for worsening of fatigue in addition to left lower limb swelling and dry cough. He complained of significant weight loss for 2 months; past and family history was unremarkable for similar complaints, hemolytic anemia, high-risk behavior, intravenous drug abuse, and tuberculosis. At presentation, he had a fever (100.5°F), tachycardia (112 bpm), and normal BP (114/76 mmHg). Apart from being severely malnourished (body mass index 16.4 kg/m^2), he had pallor and left lower limb pitting edema; liver and spleen were not palpable. Doppler ultrasound revealed left lower limb deep vein thrombosis [Figure 1]. Two-dimensional ECHO revealed 2.3 cm × 1.5 cm pedunculated mass adherent to the interventricular septum in the left ventricle [Figure 2] and no features of the right ventricular dysfunction. The left moderate pleural effusion and bilateral pleural-based pulmonary infarcts were evident on computed tomography chest [Figure 3]. He was put on subcutaneous enoxaparin. His hemogram revealed normocytic normochromic anemia (Hb 6.3 g/dL), leukopenia (total leucocyte count [TLC] 1.6 × 10^9/L), and normal platelet count (334 × 10^9/L). Work up for paroxysmal nocturnal hemoglobinuria was planned in view of bicytopenia with thrombosis. Meanwhile, 34% blasts and atypical promyelocytes were seen on the peripheral blood smear. Coagulation screen was unremarkable except isolated prolonged prothrombin time (24 s). Presuming the diagnosis of APML, ATRA, and ATO-based induction therapy was started promptly, and two

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units of packed red blood cells were transfused. Bone marrow examination and flow cytometry were consistent with APML (CD13+, CD33+, HLA-DR−, no aberrant expression markers) [Figure 4]. *PML-RARA* fusion gene detection by qualitative reverse-transcriptase-polymerase chain reaction (RT-PCR) confirmed the diagnosis of APML (low risk). Blood cultures were sterile; pleural fluid analysis revealed exudative pattern and no malignant cells. Investigative work up for pulmonary tuberculosis and HIV was inconclusive. Fever resolved by day 7 of induction therapy. Hemorrhage, ischemia, and differentiation syndrome were not observed during the induction therapy. The complete hematological response was achieved on day 27. End of induction bone marrow was in remission, and qualitative RT-PCR for *PML-RARA* was negative. Consolidation chemotherapy was continued along with low molecular weight heparin.

Discussion

Pathogenesis of thrombosis in APML is incompletely understood. Apart from procoagulant phenotype of leukemic promyelocytes and concomitant diffuse intravascular coagulation (DIC), ATRA-based therapy *per se* has also been thought to enhance thrombosis likelihood in such patients.[5-7] High total leukocyte count at diagnosis (> 10 × 10^9/L), *FLT3* positivity, presence of variant translocation, CD2 or CD15 expression, and occurrence of differentiation syndrome are well-known predisposing factors.[8,9] The most commonly reported thrombotic complications before APML induction are cerebrovascular accidents, DVT/PE, and cardiac thrombotic events (including myocardial infarction and intraventricular thrombosis).[4] Apart from ATO and ATRA-based therapy, these patients also require anticoagulation for the thrombus.[10-12]

The index case had an elusive presentation in the form of fever and anemia. Although the nutritional deficiency is the most common cause of anemia in developing countries, meticulous peripheral blood smear examination can pinpoint catastrophic etiologies at an early stage. There was a step-wise clinical progression with lower limb DVT followed by pulmonary embolism, pulmonary infarction, and cardiac involvement.

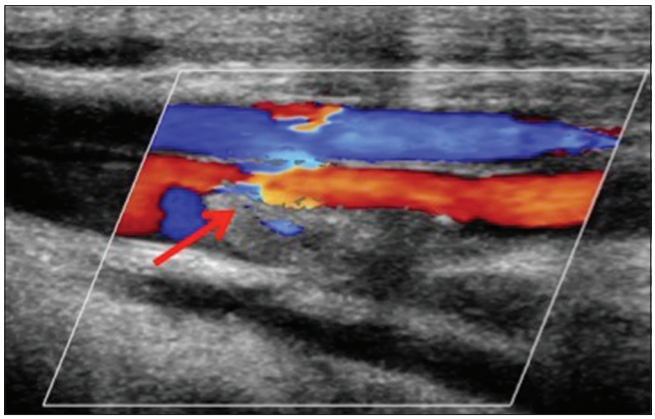

Figure 1: Doppler ultrasonography showing absence of color flow in the left common femoral vein suggestive of thrombosis

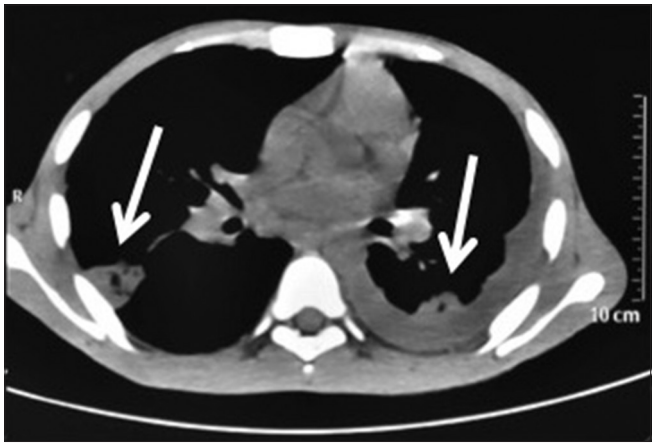

Figure 3: Computed tomography-chest showing bilateral pleural-based pulmonary infarcts with left-sided pleural effusion

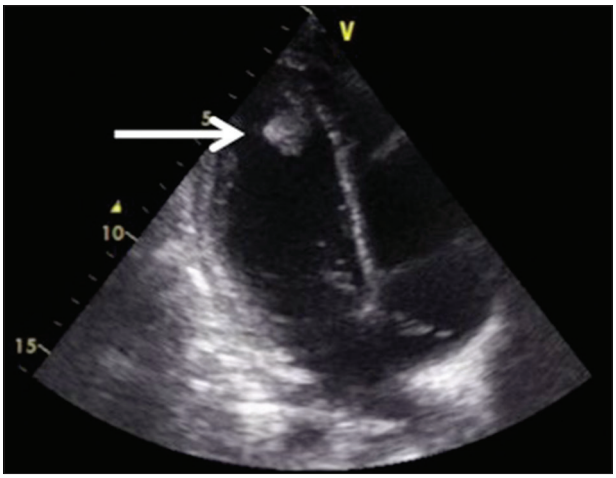

Figure 2: Two dimensional-Echocardiography showing 2.3 cm × 1.5 cm pedunculated mass within left ventricular cavity adherent to interventricular septum

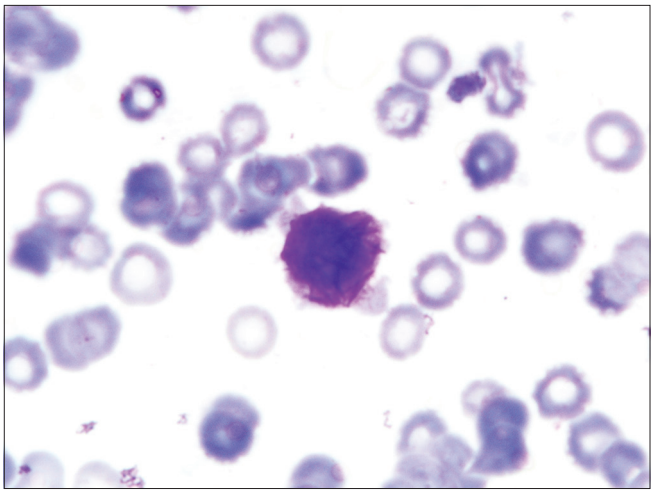

Figure 4: Bone marrow aspiration slide showing blast with multiple Auer rods (Faggot cells)

At the time of diagnosis, white blood cell (WBC) count was surprisingly low and other thrombosis predisposing risk factors were conspicuously absent (DIC, *FLT3*, CD2 or CD15 expression, and differentiation syndrome). The formation of intravascular leukemic thrombi can be offered as an explanation for low initial WBC count, but the same could not be proved by histological examination in the index case. Importantly, neither the existing thromboses worsened nor any new thrombotic events occurred during ATRA plus ATO therapy. Hence, ATRA-based induction therapy can be safely considered in APML patients who have thrombosis prior to induction therapy.

Conclusion

Hematological abnormalities should be thoroughly investigated in patients presenting with thromboembolic manifestations. Thrombosis in APML is an uncommon yet dire complication that can occur even in the absence of known risk features. Successful outcome in APML complicated by thrombosis can be achieved with ATRA plus ATO-based therapy.

Informed consent

Informed signed written consent was taken from the patient involved.

Declaration of patient consent

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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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