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CASE REPORT

Acute promyelocytic leukemia presenting as pulmonary thromboembolism: Not all APLs bleed

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ABSTRACT

We present a rare case of acute promyelocytic leukemia (APL) presenting as pulmonary thromboembolism being misdiagnosed as community-acquired pneumonia. Thrombotic phenomenon in APL are poorly understood and grossly underreported. In our case, following no response to standard antibiotic treatment, the patient was further investigated and detected to have an acute pulmonary thromboembolism following right lower limb deep vein thrombosis (DVT). Though, complete blood picture revealed only mild hyperleukocytosis, bone marrow biopsy and aspiration revealed 60% blasts and a positive t (15,17)(q22,12) and PML retinoic acid receptor alpha (RARA) fusion protein on molecular cytogenetics. He was diagnosed as APL and received treatment with all-transretinoic acid (ATRA) and arsenic trioxide (ATO) and therapeutic anticoagulation.

Key words: Acute promyelocytic leukemia, community-acquired pneumonia, pulmonary thromboembolism

INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct type of hematopoietic malignancy in the acute myeloid leukemia group. The unique cytogenetic anomaly detected is the presence of t (15,17)(q22,12), which signifies the fusion between the promyelocytic leukemia (PML) gene located on chromosome 15 and retinoic acid receptor alpha (RARA) gene at chromosome 17.[1] APL typically presents as life-threatening bleeding diathesis due to disseminated intravascular coagulation (DIC) and thrombocytopenia which, in the past was a significant cause of death due to pulmonary and intracranial bleeds.[2] Thrombotic phenomenon, though increasingly being described in literature, is poorly understood and grossly underreported. We discuss a rare case of APL mimickinga community-acquired pneumonia following pulmonary thromboembolic phenomenon.

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CASE REPORT

A 48-year-old male presented to the emergency department with complains of 2-week history of fever and dry cough. He did not complain of hemoptysis, chest pain, history of weight loss, or night sweats. He denied history of substance abuse or high risk behavior. The patient was hemodynamically stable. His physical examination was unremarkable except for harsh vesicular breath sounds at the right interscapular area. Chest rhoentogenography revealed a right mid zone consolidation. With a suspicion of probable community-acquired pneumonia, he received intravenous antibiotic therapy with ceftriaxone. Despite treatment for 1 week, the patient failed to experience any symptomatic relief. On further investigation with computed tomography

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chest, a right mid zone infarct with cavitation was detected. Pulmonary angiogram confirmed the diagnosis of a right mid zone pulmonary infarct. A venous Doppler of the lower limb was suggestive of acute deep vein thrombosis (DVT) involving the right popliteal vein.

Routine blood tests revealed anemia (hemoglobin: 10.5 g/dL), mild leucocytosis (total leucocyte count (TLC):14,800 cell/mm^3 and 78% neutrophils) and an abnormal left shift. The liver and renal function tests were normal. Coagulation profile showed normal prothrombin and activated partial thromboplastin time; normal fibrinogen, homocysteine levels; absence of factor C, S, antithrombin deficiency or factor V Leiden mutation; and a D-Dimer level of 1,418 ng/ml (normal: 0–233 ng/ml). Failing to find a possible cause of thrombosis, we performed a bone marrow biopsy and aspiration which revealed 60% blasts positively staining with myeloperoxidase. Molecular cytogenetics was positive for t (15,17)(q22,12). PML RARA fusion protein was positive. A diagnosis of APL with right lung infarct and cavitation following pulmonary thromboembolism from right lower limb DVT was made.

He received low molecular weight heparin (LMWH) and later warfarin as part of treatment for pulmonary embolism. He was promptly started on induction therapy with all-transretinoic acid (ATRA) and arsenic trioxide (ATO) without any complications and achieved molecular complete remission with PML RARA documented to be negative after 1 month of therapy. He completed six courses of maintenance therapy with ATRA and ATO. A repeat PML RARA quantitative analysis confirmed complete remission. He has been on regular follow-up since then and has not suffered from any recurrence of the thromboembolic event.

DISCUSSION

The PML RARA gene formed after fusion between PML gene on chromosome 15 and RARA gene on chromosome 17 leads to the formation of PML-RARA protein which promotes excessive production of promyelocytes in the marrow.[3] APL was previously known to have an aggressive course with median survival lasting not more than a month. However, with the advent of ATRA and ATO, we no longer witness such dismal figures with about 90–95% of the patients achieving complete remission.[4] Bleeding is the most common manifestation of APL-related coagulopathy. The molecular properties of the leukemic cells are responsible for this phenomenon by releasing numerous mediators that have the potential to activate the coagulation system. The mechanisms of bleeding in APL are DIC, direct proteolysis of proteins, and hyperfibrinolysis. This is potentiated by concomitant thrombocytopenia.[2] In comparison, the occurrences of thrombotic complications are less common and grossly underreported. Thromboembolic episodes can occur due to APL, following induction therapy with ATRA and during ATRA syndrome.[2] The exact pathogenesis of thrombosis continues to remain incompletely understood and controversial. It has been postulated to be due to interactions between the host defense mechanisms and the promyelocytes. Release of prothrombogenic particles including tissue factor, inflammatory cytokines, and expression adhesion molecules on the surface of tumor cells have been implicated.[5] In addition, there is evidence that demonstrates a higher expression of tissue factor in APL in comparison to other leukemias.[6] Breccia *et al*., proposed higher white blood cell (WBC) counts, fms-like tyrosine kinase, internal tandem duplication (FLT3/ITD) mutation, the type of PML/RARA transcript, and a positive CD2/CD15 expression to be associated with higher incidence of thrombosis.[7]

The clinical manifestations of APL-related thrombosis are florid. It ranges from cardiac involvement with reports of acute myocardial infarction, intraventricular thrombosis and subendocardial ischemia, to cerebrovascular accidents and DVT/pulmonary embolism. Other less common sites of involvement are renal artery thrombosis, acute limb ischemia, and hepatic and portal vein thrombosis. Rashidi *et al*., recently reviewed the 94 cases in literature of major APL-related thrombosis. They observed >80% of the thrombotic events occurring before or during induction therapy.[8]

In this case, our patient presented as fever and dry cough, prompting the suspicion of a respiratory tract infection. The diagnosis was further delayed due to absence of both significant leukocytosis and blasts in the complete blood picture. The absence of any symptomatic recovery in the patient despite 1 week of antibiotic therapy made us investigate further. Nevertheless, once diagnosed as APL, he was promptly started on combination therapy with ATRA and ATO.

To conclude, thromboembolic events are not unknown but less frequent than bleeding manifestations in APL. Though bleeding manifestations continue to remain the focus of attention, the incidences of thrombotic complications are on the rise. There continues to remain lacunae in our knowledge regarding the trends of thrombosis and risk factors analysis that promote increased thrombosis. We also highlight this unusual cause of thromboembolism which can easily be misdiagnosed in routine general practice. A high degree of suspicion and awareness of such rare presentations would help overcome such diagnostic challenges and facilitate specific management. We emphasize this rare

presentation of APL presenting as pulmonary embolism, being misdiagnosed as pneumonia. To the best of our knowledge, this is the first such case reported in Indian literature of this phenomenon.

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Conflicts of interest
There are no conflicts of interest.

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