A Rare Occurrence of Simultaneous Venous and Arterial Thromboembolic Events – Lower Limb Deep Venous Thrombosis and Pulmonary Thromboembolism as Initial Presentation in Acute Promyelocytic Leukemia

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ABSTRACT: The development of acute myeloid leukemia has been attributed to various factors, including hereditary, radiation, drugs, and certain occupational exposures. The association between malignancy and venous thromboembolism events is well established. Here, we present a case of a 70-year-old Indian man who had presented with arterial and venous thrombosis, and the patient was later diagnosed with acute promyelocytic leukemia (APL). In our case, the patient presented with right lower limb deep venous thrombosis and pulmonary thromboembolism four months prior to the diagnosis of APL. Although thromboembolic event subsequent to the diagnosis of malignancy, and especially during the chemotherapy has been widely reported, this prior presentation with simultaneous occurrence of both venous and arterial thromboembolism has rarely been reported. We take this opportunity to state the significance of a complete medical evaluation in cases of recurrent or unusual thrombotic events.

KEYWORDS: malignancy, acute promyelocytic leukemia, arterial and venous thrombosis, anticoagulation

Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML). It is named as AML-M3 by the French–American–British classification system according to morphological features. Cytogenetically, APL is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, which results in the fusion between retinoic acid receptor and promyelocytic leukemia gene. The development of AML has been attributed to various factors, including hereditary, radiation, drugs, and certain occupational exposures. The association between malignancy and venous thromboembolism events is well established. The pathogenesis of the prothrombotic state in malignant disorders is complex and reflects the involvement of different mechanisms, including activation of blood coagulation by tumor cells via procoagulant substances, impairment of fibrinolytic pathways, and alterations of endothelium favoring a thrombogenic state. 1,2 Both arterial and venous thromboembolisms (VTEs) occurring simultaneously is an uncommon event and very few diseases are known to present with it. Among various causes, myeloproliferative disorders, antiphospholipid syndrome, malignancy-associated thrombosis, and heparin-induced thrombocytopenia are some of the notable causes. 3

In this case report, we report an unusual combined arterial and venous thrombosis as the initial presentation in a patient who was later diagnosed with APL. The patient has given his consent for publication of this report.

Case Report

A 70-year-old male was referred from another city hospital to our tertiary care center. The patient, at the time of presentation, complained of left-sided sharp chest pain, fever with scanty, nonpurulent sputum for 10 days, and swelling and pain over the right leg for the past one week. On taking the complete history of the patient, the patient was apparently retired 10 years ago. He was admitted and investigated. Serial chest X-rays revealed heterogenous opacity involving the left lower zone and the left middle zone, followed by cavitary lesion without any air fluid level in it. Venous Doppler right lower limb revealed noncompressible external iliac, common femoral, superficial femoral, long saphenous, and short saphenous, indicating thrombosis. With respect to the above...
findings, the patient was then referred to a higher center, and thus presented to us. He was examined, and respiratory examination revealed bronchial breath sounds in the left middle zone with decreased air entry in the left basal area anteriorly. Lower limbs showed no sign of any ulceration or skin or color changes. Chest X-ray revealed heterogeneous opacity with central cavitation and air fluid level seen within the left mid zone, suggestive of lung abscess with adjacent consolidation. Venous Doppler right lower limb revealed similar findings as the previous one. Pleural fluid analysis revealed the following: total leukocyte count (TLC) 1,400/mm$^3$, polymorphs 90%, lymphocytes 10%, glucose 107 mg/dL (spot blood sugar – 128 mg/dL), and protein 5.4 g/dL. Sputum sample for acid fast bacilli 1 and 2 was negative. Blood investigations revealed the following: hemoglobin (Hb) 11.5 g/dL, TLC 4,900/mm$^3$, polymorphs 36%, lymphocytes 60%, eosinophils 2%, monocytes 2%, platelet count 2.27 lac/mm$^3$, serum homocysteine is within normal levels, and antiphospholipid antibodies IgM and IgG are negative. Reference range taken as normal values for aforementioned parameters were Hb 13.3–16.2 g/dL, TLC 3,540–9,060/mm$^3$, polymorphs 40%–70%, lymphocytes 20%–50%, monocytes 4%–8%, eosinophils 0%–6%, basophils 0%–2%, and platelet count 1.65–4.15 lac/mm$^3$.

Contrast-enhanced computed tomography (CT) of thorax revealed right and left pulmonary artery segmental branches thrombosis with peripheral wedge opacities in both lungs, one of them showing cavitations like infarcts (Fig. 1). Two-dimensional echocardiography revealed mild concentric left ventricular hypertrophy with mild tricuspid regurgitation with type II diastolic dysfunction, there was borderline right atrium and right ventricular dilatation with an ejection fraction of 60%.

Patient was managed conservatively for right lower limb deep venous thrombosis (DVT) with pulmonary thromboembolism (PTE), and the patient was discharged to outpatient department for follow-up and was asked to administer 05 mg once daily (OD) warfarin tablet on maintained international normalized ratio. However, he was lost to follow-up after one month. After two months, he suddenly reappeared again, and this time presented with sudden onset progressive dyspnea for the last three days. Patient had blood pressure of 116/70 mmHg, heart rate of 108 per minute, and respiratory rate of 32 per minute. Arterial blood gas analysis revealed respiratory alkalosis. He had stopped all treatment after he was lost to follow-up. A suspicion of massive acute on chronic PTE was made and urgent CT angiography was done.

CT pulmonary angiography revealed main pulmonary artery (30 mm) with no filling defect, right pulmonary artery (22 mm) and left pulmonary artery (20 mm) with well-defined hypodense filling defect seen in distal most part of right and left pulmonary arteries extending into their segmental branches suggestive of PTE (Fig. 2). Venous Doppler examination of both lower limbs showed no evidence of thrombosis. The patient was promptly thrombolysed with streptomycin as per protocol with a 150,000 international units (IU) infusion over 30 minutes followed by infusion of 100,000 IU per hour for 12 hours under observation and the patient improved symptomatically. Patient was then treated with heparin infusion at 1,000 IU per hour and was started on oral anticoagulation with warfarin on the third day of admission. Further investigations revealed the following: Hb 6.5 g/dL, TLC 49,240/mm$^3$, platelet count 44,000/mm$^3$, differential leukocyte count (DLC) atypical cells 95%, polymorphs 4%, and lymphocytes 1%. Peripheral smear revealed leukocytosis with the presence of a large number of atypical cells (blasts).
Cells showed high nucleus to cytoplasm ratio, opened up chromatin, and prominent nucleoli. Cytoplasm was scant with eosinophilic granules and few blasts also showed rod-like structures (Auer-rods). Red cells were normocytic normochromic, platelets were diminished, and blast cells were strongly positive for myeloperoxidase. These factors lead to the diagnosis of AML (Figs. 3–5). Flow cytometry revealed the following: cluster of differentiation (CD)34+, CD117+, CD11c+, CD13−, and human leukocyte antigen DR−. The patient was now diagnosed to have AML, M3 TYPE. Patient was managed conservatively with blood transfusions, and subsequently referred to a hematology oncology center for bone marrow transplant.

**Discussion**

APL is a distinct subtype of AML. Cytogenetically, APL is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, t(15:17). This hematological condition is characterized by the presence of atypical Promyelocytes in peripheral blood and bone marrow. APL has been known to be associated with coagulopathy, with thrombosis and bleeding being the most common presentations. These hemorrhagic complications have been well established as an important clinical feature of APL and the most common cause of early mortality.

The pathophysiology of hemorrhagic complications, especially thrombosis, although commonly associated with APL, is complex and less understood. Expression of CD2, presence of internal tandem duplications of fms-like tyrosine kinase 3 gene (FLT3-ITD), and elevated white blood cell count have been found to have significant correlation with higher incidence of thrombosis. Pathogenesis hypotheses of thrombosis in APL involve production of prothrombogenic cytokines by abnormal promyelocytes and a direct expression of tissue factor and cancer procoagulant.

In a review on APL-related thrombosis, 94 cases were studied, and the percentage of thromboembolic events that occurred prior or during the induction treatment was 84%, of which arterial involvement was found in 55% and venous events were in 45%. DVT/PTE (28.7%) was the most common event of thrombosis followed by cardiac events with 26.6% and cerebrovascular events with 21.3% incidence. Among the study population, thrombosis was the initial manifestation only in two cases. Another large cohort retrospective study on 719 patients with acute leukemia was done in which VTE was the presenting manifestation in 2.1% of the cases, with no difference between AML and acute lymphoblastic leukemia, and with an incidence of 6.5% thrombosis among patients with APL. Few theories have been put forth for the association between venous and arterial thrombosis. One hypothesis states that venous and arterial thromboses could be associated through atherosclerosis, because atherosclerosis can further activate an inflammatory reaction, and it can also activate a coagulation cascade. Although adequate research and literature on this causal association are not available, arterial thrombosis could be a result of an inflammatory response initiated by the venous thrombus.
Thus, this case has an unusual and a rare presentation of APL. Unfortunately, APL could not be detected early as the peripheral blood smear of the patient did not show any blast cell on the initial and subsequent examinations and then the patient was lost to follow-up.

Infrequently, there have been instances of the thromboembolic event occurring before the diagnosis of cancer, and thus, it has been suggested that deep venous thrombosis may be a predictor of the subsequent diagnosis of cancer, although a few studies have indicated an association, and there is a need for further research.12–14 In the recent study, 145 patients with primary venous thrombosis were observed over a period of two years and 11 cases of cancer were found as compared to 2 two cases among 105 patients with secondary venous thrombosis, representing an odds ratio of 2.3 with even higher incidence of cancer in patients with recurrent idiopathic venous thrombosis than in patients without this condition, with an odds ratio of 4.3.13 Thus, emphasizing a significant association between a thromboembolic event and a subsequent diagnosis of cancer. In another study by Nordstrom et al, 1,183 patients with DVT were studied and interpreted that the risk of cancer was found to be five times more in these patients as compared with the general population during the first six months of follow-up but no increased risk during later follow-up.14

**Conclusion**

An investigative approach should always be undertaken to find the cause of a thrombosis with thorough medical evaluation, especially in a case with unusual presentation or recurrent episodes of thromboembolic events. In this context, among other etiologies, an emphasis on prompt investigation for solid and hematologic neoplasia should be undertaken. A high index of suspicion while treating unusual thromboembolic events can significantly increase the chances of early timely diagnosis and better health care outcome.

**Author Contributions**

Conceived the concepts: ASK, PD. Analyzed the data: ASK, PD. Wrote the first draft of the manuscript: ASK. Jointly developed the structure and arguments for the paper: ASK, PD. Contributed to the writing of the manuscript: BK, AG. Agree with manuscript results and conclusions: ASK, PD, BK, AG. Made critical revisions and approved final version: ASK, PD, BK, AG. All authors reviewed and approved of the final manuscript.

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