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Chronic deep venous thrombosis as the presenting manifestation of acute promyelocytic leukaemia : A case report

Prabodh Kumar Das[1] **Rajesh Kumar Bhola**[2*]

[1]*Department of Medical Oncology/Hematology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.*
[2]*Laboratory Haematology Division, Department of Pathology, IMS & SUM Hospital, Siksha 'O' Anusandhan, Deemed to be University, Bhubaneswar, Odisha, India.*

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ABSTRACT

Background: Acute promyelocytic leukaemia (APL) usually presents with disseminated intravascular coagulation or hyper-fibrinogenolysis followed by bleeding manifestation. But thrombosis as a presenting manifestation is less often reported in APL.

Objectives: We describe an uncommon case of chronic deep venous thrombosis (DVT) of lower limb with unsuspected APL.

Results: A 27 year old male presented with DVT and was treated with enoxaparin and later Dabigatran for 2 months without any improvement. A routine haematological assessment showed Leucopenia with few circulating abnormal promyelocytes. The bone marrow assessment with flow cytometry and molecular studies established the diagnosis of APL. Patient was never having any bleeding manifestation despite on anticoagulation too. A thrombophilia work up revealed presence of hyper-homocysteinemia and mild lupus anticoagulant in addition to APL as a prothrombotic event.

Conclusion: DVT with leukopenia warrants further investigation to rule out Acute Promyelocytic Leukaemia. It includes a thorough peripheral smear examination to look for few circulating abnormal promyelocytes, bone marrow studies and molecular /cytogenetics analysis.

Introduction

Acute promyelocytic leukaemia (APL) is one of the subtypes of acute myeloid leukaemia (AML) with high cure rate as well as high mortality. It commonly presents with bleeding manifestation and disseminated intravascular coagulation (DIC) which is responsible for early death. Comparatively thrombosis is not a very common manifestation and most commonly presents during recovery phase from chemotherapy. But, thrombosis especially chronic deep venous thrombosis (DVT) as an initial manifestation is still rare with few case reports in literature.[1] We report such a rare case of unprovoked chronic DVT in a young adult with APL. Additional prothrombotic risk factors like hyper-homocysteinemia and transient mild positive lupus anticoagulant were identified.

Case report

A 27 year old male evaluated outside for the complaint of sudden onset unprovoked pain and swelling of right calf for the past 10 days.Professionally being an academician he had relatively sedentary lifestyle with long hours of computer work. He was born of non-consanguineous marriage with no significant family history of thrombophilic risk factors. He was taking many ayurvedic medications. The

* **Corresponding author.**
Author's Address: *Laboratory Haematology Division, Department of Pathology, IMS & SUM Hospital, Siksha 'O' Anusandhan, Deemed to be University, Bhubaneswar, Odisha, India.*
** **E-mail address:** rajeshkumarbhola@soa.ac.in
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physical examination revealed swelling and tenderness of right calf. No hepatosplenomegaly or lymphadenopathy noted. The systemic examinations were within normal limits.The right lower limb venous system Doppler showed hypoechoic thrombus filling the lumen of vein extending from mid superficial femoral vein till distal posterior tibial vein distally extending through sapheno-popliteal junction in the small saphenous vein suggestive of DVT. The chest X-ray and abdominal ultrasound didn't elicit any abnormality. He was started on injection low molecular weight heparin (LMWH) enoxaparin 60 mg twice a day for 2 days followed by Dabigatran 150 mg twice a day for 2 months. But the DVT didn't resolve clinically with persistent leg swelling.

He was referred for haematology consultation after 2 months for non-resolving DVT despite on anticoagulants. He was haemodynamically stable with unremarkable physical examination. The laboratory investigations revealed following findings. The complete blood count revealed leukopenia with Hb 11.6 gm/dL, WBC count $1.62x10^3$/µL, platelet count $106x10^3$/µL, RBC count $3.5x10^6$/µl, PCV 32.2%, MCV 92 fL, MCH 33.1 pg, MCHC 36 gm/dL, RDW-SD 47.7 fL, RDW-CV 14.6%, reticulocyte count 0.92%. The peripheral smear showed normocytic normochromic blood picture with macrocytes, tear drop cells and few fragmented RBC. We reviewed the whole slide in search of abnormal cells. Interestingly it also elicited 3 % abnormal promyelocytes with occasional faggots (Figure 1A). The liver function tests were normal with total bilirubin 0.37 mg/dL, bilirubin (direct) 0.12 mg/dL, alkaline phosphatase 117.0 IU/L, SGOT 17.50 IU/L, SGPT 16.30 IU/L, total protein 8.45 gm/dL, albumin 4.95 gm/dL. The vitamin B12 levels were >2000 pg/mL. The renal function tests were also within normal limits with creatinine 1.19 mg/dL, urea 15 mg/dL. The uric acid levels were 5.30 mg/dL with no evidence of hyperuricemia. The screening for hepatitis B, hepatitis C and HIV were negative.

In view of leukopenia with few circulating abnormal promyelocytes, a possibility of acute promyelocytic leukaemia was considered with review of clinical history and physical examination for any specific bleeding manifestation. Still we couldn't elicit any features of active or past bleeding since presentation. A bone marrow aspiration was done which showed 66% abnormal promyelocytes with hyper-granular cytoplasm and faggots and strong myeloperoxidase stain positivity (Figure 1B and 1C). A flow cytometry assessment was performed. The gated population showed moderate CD45 positivity with intermediate side scatter (SSC) and were positive for cytoplasmic MPO, CD117, CD13, CD33, CD38 (subset 52%), CD58 while were negative for CD34, nuclear TdT, HLA DR, CD19, CD79a, membrane CD3, cytoplasmic CD3, CD7, CD64, CD11c, CD14, CD56, CD36, CD4, CD2, CD16, CD15, CD10 (Figure 2). A conventional cytogenetics showed t(15;17)(q22;12) and reverse transcriptase showed PML-RARA positivity with bcr1 transcript (Figure 1D). A diagnosis of acute promyelocytic leukaemia with PML-RARA was rendered.

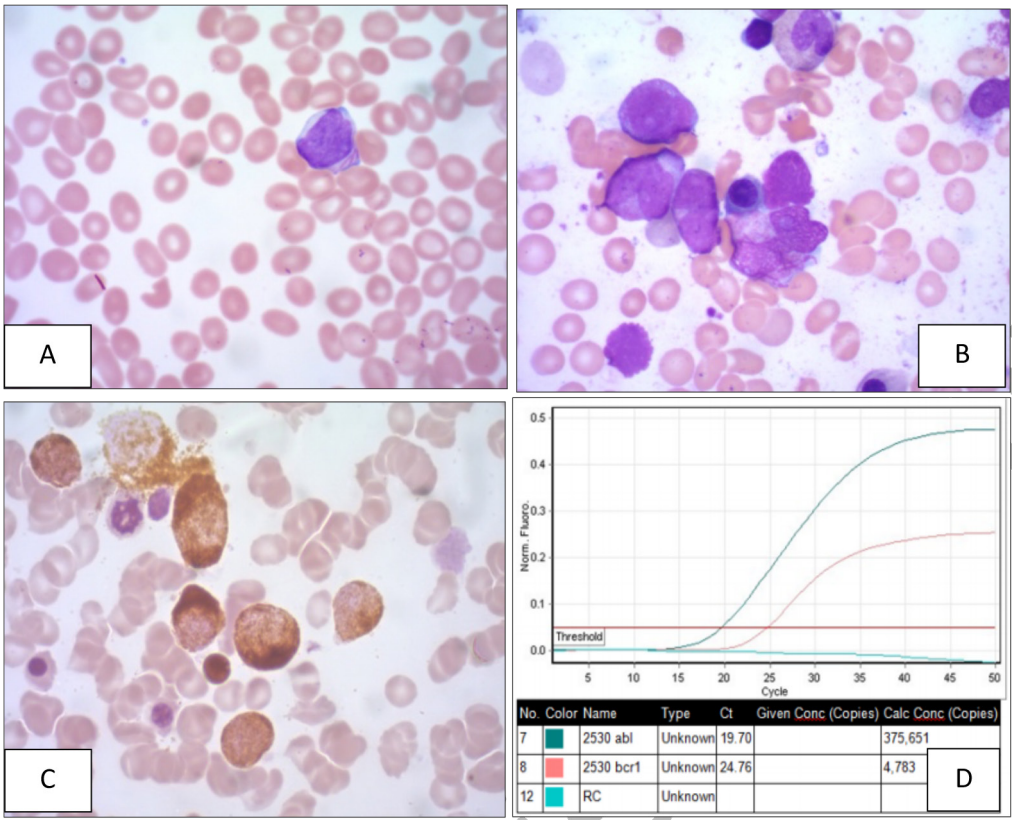

Figure 1. *Peripheral smear Shows a promyelocyte with faggot (Leishman Giemsa stain, oil immersion field 1000X)(A), Bone marrow aspiration smear shows abnormal promyelocytes with faggots (Leishman Giemsa stain, oil immersion field 1000X) (B). Promyelocytes are strong myeloperoxidase positive (MPO stain, oil immersion field 1000X) (C). RT PCR showing t(15;17) PML-RARA bcr-1 transcript (D).*

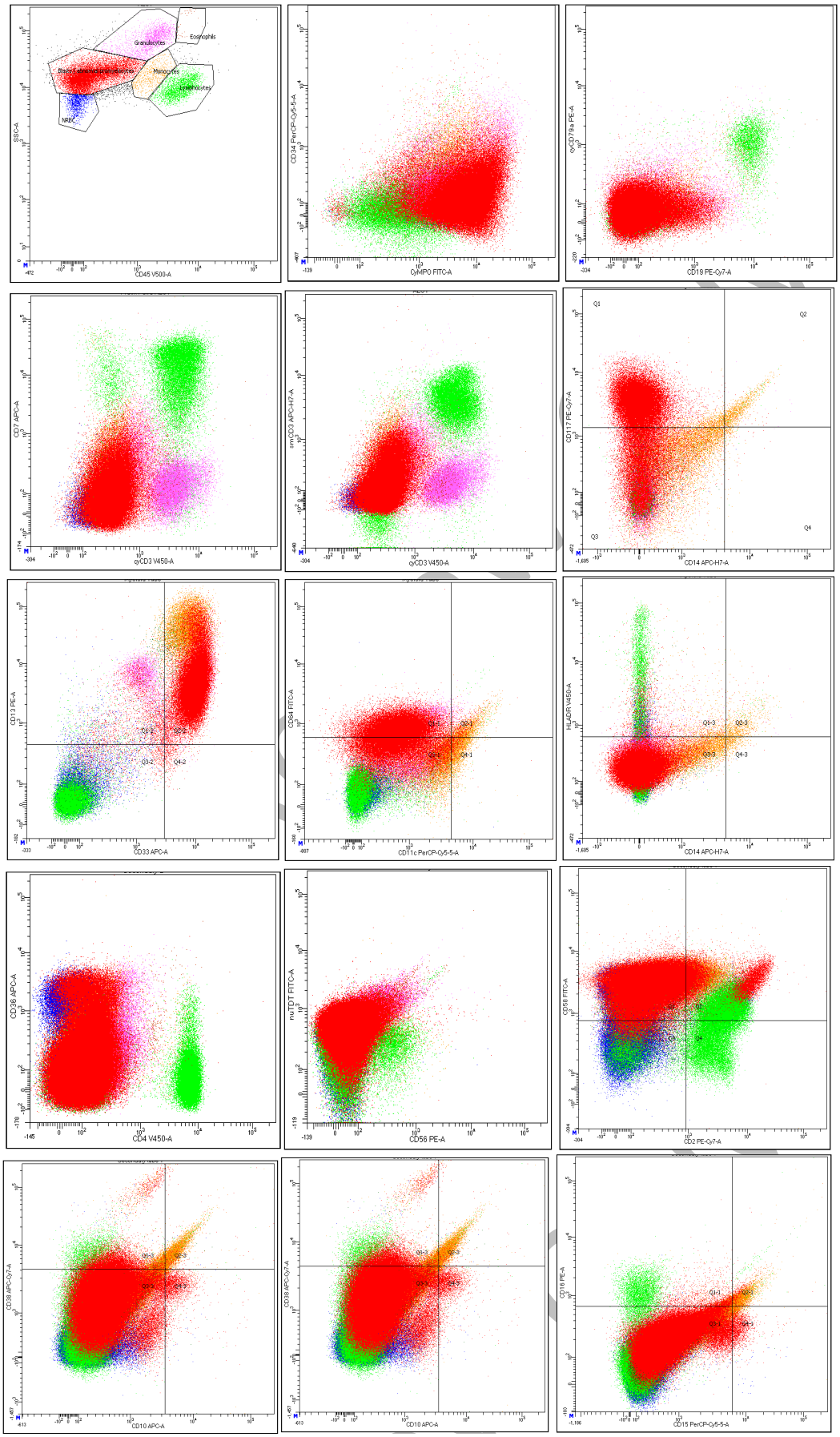

Figure 2. *Flow cytometry assessment on BD FACSCanto II 3 Laser 8 color flow cytometry and analyzed by FACSDiva 2.1 software shows the promyelocyte/ blasts gate on moderate CD45 with intermediate side scatter (SSC) population which is positive for cytoplasmic MPO, CD117, CD13, CD33, CD58, CD64 (dim) while negative for CD34, nuclear TdT, HLA DR, CD19, CD79a, membrane CD3, cytoplasmic CD3, CD7, CD64, CD11c, CD14, CD56, CD36, CD4, CD2 CD16, CD15, CD10, CD38.*

We further evaluated for prothrombotic or bleeding risk factors. The prothrombin time (PT) 12.2 seconds (Reference interval 9.4-11.4 sec), activated partial thromboplastin time (aPTT) 32.2 sec (RI 21.4-29.0 sec), thrombin time 23.9 sec (RI 14-21 s), Fibrinogen 246.8 mg/dL (200-400 mg/dL). D-dimer was elevated with 2.53 µg/L fibrinogen equivalent unit (FEU) (Reference cut off <0.5 µg/L FEU) which was indicative of ongoing thrombosis. The assessment for inherited thrombophilic risk factors showed mild hyperhomocys teinemia with Homocysteine levels 20.76 µmol/L (RI 5.46-16.20) with normal levels of protein C 65%, free protein S 77%, factor VIII 154%). Thesickling test was negative. The assessment for acquired thrombophilia showed mild positivity for lupus anticoagulant with a Dilute Russell's Viper Venom Time (DRVVT) screen by confirm ratio of 1.31 (RI<1.2).

Patient was started on chemotherapy with all-trans retinoic acid (ATRA) 45 mg/m^2 plus Arsenic trioxide (ATO) 0.15 mg/kg IV for 5 days a week in induction phase followed by consolidation with some modifications and injection dexamethasone 10 mg/m^2 12 hourly for prevention of differentiation syndrome until end of induction therapy. He didn't develop differentiation syndrome during the therapy. He achieved post induction morphological remission. DVT resolved completely. He is doing well with 2 years of follow up without any relapse of APL or recurrence of DVT.

Discussion

The acute promyelocytic leukaemia (APL) is classically known for bleeding issues, especially due to disseminated intravascular coagulation (DIC) or secondary hyperfibrinolysis. Paradoxically thrombotic events complicating APL is a rarely reported events. In one of the series, *M Breccia et al* have reported an incidence of 8.87% (n=11) of major thrombotic events in 124 APL cases.[2] One of the largest series of 94 cases of APL with thrombosis was reviewed by Rashidi *et al*. They found that 40.4 % (n=38) developed thrombosis before initiation of therapy, 43.6% (n=41) during induction therapy.[3] The common thrombotic events include DVT or pulmonary embolism (PE), myocardial infarction (MI), and stroke. Cerebral venous sinus thrombosis, hepatic vein thrombosis, acute limb ischemia, splenic infarction, portal vein thrombosis, renal artery thrombosis or more than one thrombotic events though rare but have also been reported in literature.[3-8] But a thorough literature survey didn't show any evidence of chronic DVT as a presenting manifestation of APL.

The ATRA therapy was also associated with an increased risk of thrombosis as high as 16%. It has been postulated that ATRA causes an imbalance between procoagulant and fibrinolytic forces which possibly induces a prothrombotic state. ATRA causes upregulation of cytokines production leading to persistent mild increased coagulation activation markers. Although in literature, there are several case reports of thrombosis and APL but the number of cases with thrombosis especially chronic DVT as presenting manifestation of APL are a few.

The risk factors for developing thrombosis in APL included a higher leukocyte count, immunophenotypic expression of CD2&CD15, prevalence of the bcr3 transcript type, and expression of FLT3-ITD. The order of frequency of sites is deep vein thrombosis, sub-endocardiac ischemia, and intraventricular thrombosis. A low fibrinogen <170 mg/dL; anaemia (haemoglobin>10 gm/dL), M3 variant subtype are the other risk factors of thrombosis. But contrary to it, our case showed Sanz low risk with low WBC count, normal platelet count, negative for CD2 and CD15 and PML-RARA *bcr1 transcript*.

In order to analyse the non-leukemic prothrombotic risk factors, we found hyperhomocysteinemia and mild positive lupus anticoagulant in our case. There are few reports of acute myeloid leukemia especially APL with hyperhomocysteinemia causing thrombosis.It has been observed in a murine model of APL that Methionine-induced hyperhomocysteinemia could revert the fibrinolytic pathway activation.[9] Hence we feel that hyperhomocystenemia in our case might be the cause of thrombosis and non-development of bleeding due to DIC or hyperfibrinolysis and remained undiagnosed for 2 months. But the cause of hyperhomosys-teinemia can be hereditary or due to disturbed metabolism of homocystein as seen in cancer as we couldn't do any molecular studies.[10] Similarly few case reports have been described about AML with coexisting antiphopholipid syndrome but specifically APML with lupus anticoagulant are scarce.[11-13]

Our case is rare in many aspects and provides major input regarding approach to cases with unprovoked DVT and leukopenia. It shows that an unprovoked DVT may mask and delay the diagnosis of APL especially low risk groups. The peripheral smear with unexplained leukopenia requires a thorough evaluation of the whole slide which may be lifesaving in a scenario of APL which is otherwise highly fatal. In addition all cases of thrombosis in APL should be searched for other additional inherited or acquired prothrombotic risk factors. Possibly we are describing the first case of chronic DVT as the presenting manifestation of APL with additional leukaemia associated hyperhomocysteinemia and mild lupus anticoagulant.

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