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Case Report

Complex Arterial and Venous Thrombosis in Polycythemia Vera: what Does Leukocytosis Predict?

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ABSTRACT

Thromboembolic events represent the main cause of morbidity and mortality in patients with polycythemia vera. Leukocytosis has been identified as an important risk factor for development of vascular thrombosis. A 47-year-old woman with polycythemia vera presented with pain and swelling in her right calf. She was scheduled to receive anagrelide which was effective on polycythemia and thrombocytosis, but leukocytosis persisted. She was diagnosed with thrombosis in right popliteal vein and left common femoral vein by duplex ultrasonography. We suggested a role for leukocytosis in inducing thrombotic phenomenon in our patient with polycythemia vera.

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Introduction

Polycythemia vera (PV) is a Ph-negative myeloproliferative disorder characterized by augmented erythropoiesis and resultant manifestations, predominantly thrombotic events and related complications.[1] Numerous factors contribute to thrombosis in PV, such as increased whole blood viscosity, red blood cell adhesiveness, thrombocytosis, leukocytosis, impaired fibrinolytic activity, and hyperactive JAK (Janus kinase) signaling.[2] Herein, we report a case of recurrent thrombotic complications in a patient with PV who and permanent leukocytosis during cytoreductive therapy.

Case Report

A 47-year-old woman presented to our clinic complaining of dull pain and swelling of her right leg. She also complained of worsening dyspnea for the last week. She had suffered from acute coronary syndrome (ACS) and cardiac arrest six months earlier, so that a complex PCI was performed for the patient. She was a known case of PV whose further workup had revealed a positive mutation on BCR-ABL and JAK-2 Kinase on V617F gene. She was receiving anagrelide as cytoreductive therapy. Following her initial treatment with anagrelide, complete blood count revealed a good response on hemoglobin, hematocrit, and platelets, but leukocyte count remained elevated for several months (WBC count >15,000/µL).

On physical examination, the apical impulse was laterally displaced, and there were rales on the bilateral basal lung fields. There was a remarkable asymmetric edema on left lower extremity associated with warmness on palpation. Blood work on admission showed hemoglobin: 9.7 g/dl, hematocrit: 31.6%, WBC: 16,800/µL, platelet: 279,000/µL and serum creatinine: 1.12 mg/dL. Transthoracic

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echocardiography showed moderate mitral regurgitation, dilation mof all chambers, decreased left ventricle ejection fraction, left ventricle akinesis and decreased right ventricular systolic function. Hemodynamic parameters showed increased pulmonary capillary wedge pressure (PCWP: 18 mmHg), systemic vascular resistance (SVR: 1848 dynes.sec/cm^{-5}) and estimated right atrial pressure (est RAP: 15 mmHg). Duplex ultrasonography (DUS) showed a thrombus on right popliteal vein (0.32×0.25 cm) (Figure 1).

She was then treated with compressive stocking, fondaparinux, dual antiplatelets, diuretics, and angiotensin-converting-enzyme inhibitors. Her cytoreductive therapy was changed to hydroxyurea. The other day, she developed a similar complaint on the contralateral leg. A repeat DUS revealed new thrombi in left common femoral vein (0.30×0.15 cm) and left popliteal vein (0.36×0.10 cm) (Figure 2). Fondaparinux was continued for seven days when the patient was discharged home. A routine visit to cardiology clinic showed complete thrombus resolution and no further thrombotic complications after two months (Figure 3). The patient's consent was obtained for reporting the case.

Discussion

Thrombotic complications are a major cause of morbidity and mortality in patients with PV. Published data indicate that thrombosis is the most common presenting feature in PV patients ranging from 12%-49%, occurring in up to 40% during the course of the illness, and was the cause

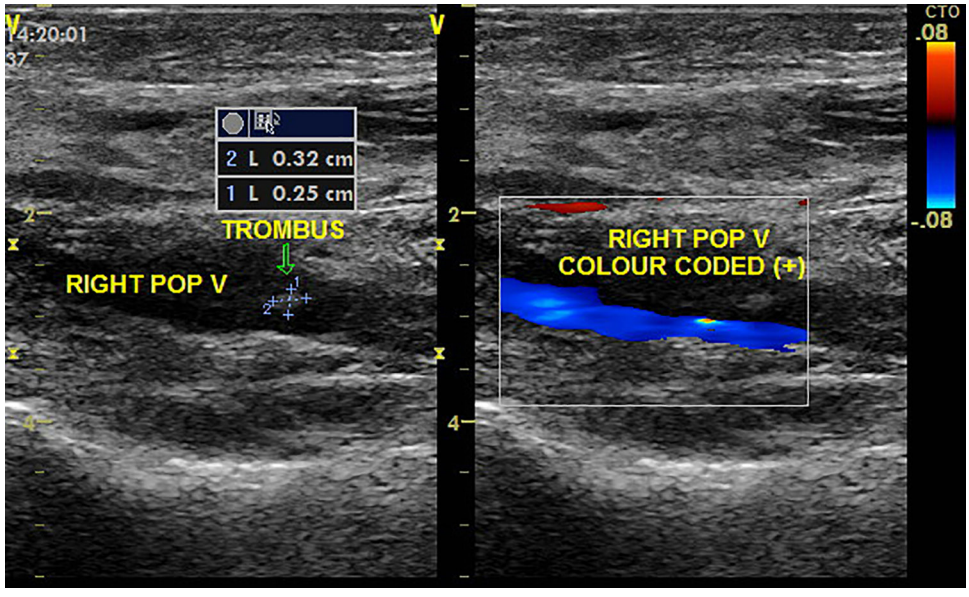


Figure 1: DUS at admission showed right popliteal vein thrombus. DUS: duplex ultrasonography.

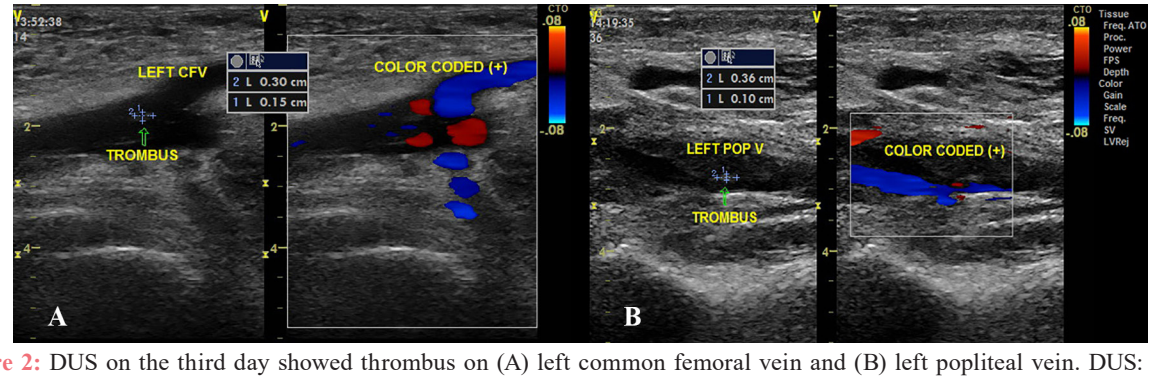


Figure 2: DUS on the third day showed thrombus on (A) left common femoral vein and (B) left popliteal vein. DUS: duplex ultrasonography.

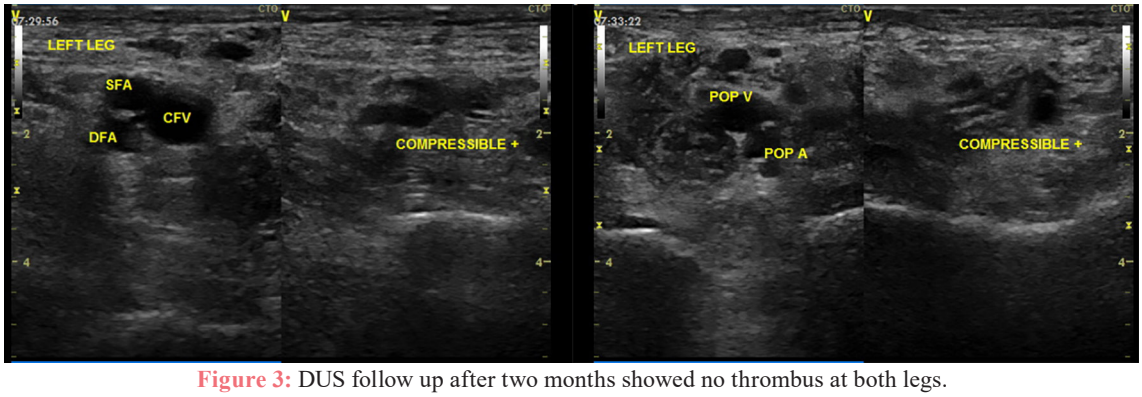


Figure 3: DUS follow up after two months showed no thrombus at both legs.

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of death in 20%-40%.[3] As one of the largest prospective cohort trials composed of 1638 patients, the prevalence of thrombosis in European Collaboration on Low-dose Aspirin in PV (ECLAP) study was 39% (29% arterial and 14% venous).[2]

In our case report, a patient with PV with a past history of primary PCI for ACS exhibited clinical symptoms and signs of deep vein thrombosis with subsequent re-thrombosis on contralateral leg. Despite normalization of polycythemia and thrombocytosis, her leukocyte counts remained elevated during the cytoreductive therapy.

Risk factors for thrombosis in an individual with polycythemia vera as described in ECLAP study were age >65 years, history of thrombotic complications, congestive heart failure, active or remote smoking, hypertension, and leukocyte count >15×10^9/L.[1] Cytoreductive therapy in PV also explained the likelihood of recurrent thrombosis in younger patients (<60 years) with leukocytosis.[4] On the contrary, main risk factors for recurrent arterial or venous vascular events in the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) study were prior arterial and venous thrombosis.[2]

The gene-dosage hypothesis suggests that allele burden determines disease severity in PV. Correlation between JAK2 V617F mutant alleles and disease phenotype is shown in Figure 4. Thrombosis, myelofibrosis transformation, pruritus, and splenomegaly are more commonly observed in highest allele burden quartile (≥75%). Lower allele burdens have been shown to result in thrombocytosis. Erythrocytosis and leukocytosis clinical phenotype also correlate with higher allele burden.[5]

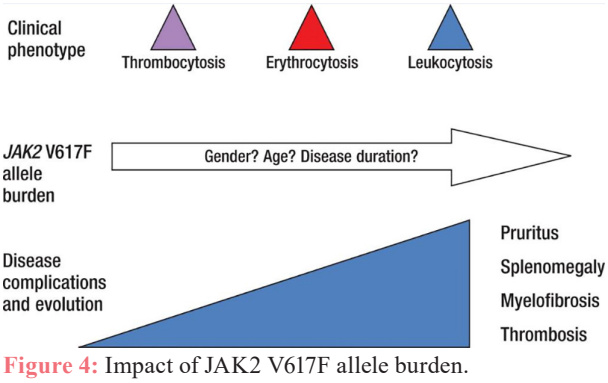


Figure 4: Impact of JAK2 V617F allele burden.

Besides hyperviscosity caused by increased hematocrit, thromboxane A2 hyperproduction, endothelial dysfunction, and platelet and leukocyte activation are likely to be involved in the pathogenesis of thrombotic diathesis in PV.[1] Leukocytosis-induced thrombophilic state in polycythemia vera was achieved through various polymorphonuclear (PMN)-derived proteases including PMN-elastase, leukocyte alkaline phosphatase, myeloperoxidase, and cathepsin G.[6] These proteases may impair natural antithrombotic mechanisms such as inactivation of tissue factor pathway inhibitor, protein C, protein S, antithrombin, and heparin cofactor II. Mixed aggregates composed of olymorphonuclear-platelet adhesion is initiated by increased expression of surface adhesion molecules, including integrins (e.g., CD11b/CD18) and selectins (e.g., L-selectin) by neutrophils.[7] A similar prothrombotic mechanism involving leukocyte-platelet aggregates has been hypothesized for other high risk thrombotic vascular diseases (i.e., stroke, hemodialysis, cardiopulmonary bypass, venous stasis ulceration, unstable angina, and cardiac infarction).[8, 9]

Neutrophils contribute to blood clotting through mixed aggregate mechanism involved in activated PMNs and platelet adhesion. Platelet activation results in the transfer of P-selectin receptor on platelet plasma membrane. After generating a tether with its ligand on leukocytes through P-Selectin Glycoprotein Ligand-1 (PSGL-1), activation through the release of their intracellular granule contents occur. In addition, activated PMNs can bind to platelets in a dynamic process, which reflects the activation of both platelets and leukocytes. The β2-integrin CD11b expressed on the cell membrane of activated PMN plays a relevant role in binding to platelets.[6] This initial cell activation results in P-selectin transfer from platelet and/or endothelial cell granules on the respective cell surface. P-selectin is an adhesive molecule, that besides generating a tether with PSGL-1, its counterreceptor on leukocytes, induces a signal, which activates leukocytes through a molecular cascade of tyrosine kinases and PI3 kinases/AKT pathway may modulate actin and cytoskeleton proteins and finally inducing beta-2 integrin Mac-1 activation and expression on leukocytes plasma membrane. The ligands of adhesion molecule Mac-1 include GpIbα, LLG-containing proteins (VWF, ICAM-1), and the RGD-containing proteins (fibrinogen, vitronectin), which help to form stable mixed aggregates adhesions. Thus, the main role in heterotypic conjugates of platelets with leukocytes in mixed aggregates involved P-selectin/beta-2 integrin interaction.[10]

Treatment of PV is mainly aimed at reducing the risk of thrombosis and bleeding, minimizing the risk of transformation to post-polycythemia myelofibrosis and acute myeloid leukemia, and ameliorating the burden of symptoms. Suppression of myeloproliferative activity using cytoreductive agents and reducing thrombotic risk need a tailored therapy to suit the clinical needs of patients based on risk-benefit ratio assessment.[11]

In our patient, aggressive treatments may provide additional benefits, but balancing the thrombotic, neoplastic, and hemorrhagic risk of the various drugs combinations remained a major challenge of treatment strategy.[1] She was treated with anagrelide which acted as a platelet function inhibitor and selective inhibitor of platelet production. Despite the reduction in platelet and hematocrit level, vascular complications occurred. We suggest that in our patient, leukocytosis had some contribution in the development of vascular complications as a reflection of the inflammatory process.

PV patients present with a wide range of hemorrhagic and thrombotic manifestations. Therefore, balancing the thrombotic, neoplastic, and hemorrhagic risk of the various drug combinations remains a major challenge of its treatment strategy.[12] Our patient was treated with short term fondaparinux. Oral anticoagulation was not given due

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to history of upper GI bleeding in the patient. The strategy to reduce her thrombosis risk was based on her persistent elevated leukocyte count with no sign of infection. The hypothesis of mixed aggregates involving leukocytes with atherothrombosis risk has led to considering short-term hydroxyurea therapy in subjects with very high vascular risk.[12] Hydroxyurea with unique antithrombotic profile not shared by anagrelide based on an experimental study has been reported in essential thrombocythemia.[1]

In vitro study by Falangaand colleagues showed the superiority of aspirin plus hydroxyurea to aspirin alone in decreasing PMN-platelet aggregates. Aspirin inhibits arachidonate acid metabolism and leukotriene production from PMNs. Its dual-action may result in decreased PMN-platelet adhesion.[6]

Conclusion

Thrombotic events in hyperviscosity due to polycythemia vera is a well known significant and devastating complication. Comprehensive management of polycythemia vera, switching from various cytoreductive therapy, and standard antiplatelet-anticoagulation for the treatment of venous and arterial thrombosis are of utmost importance to achieve successful management of these lethal complications.

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Conflict of Interest: None declared.

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