CASE REPORT

Unusual Involvement of the Portal Vein in Polycythemia Vera-Genetic Perspective

Tabinda Hasan[1], Erwa El Makki[2]

[1]Assistant Professor, Department of Anatomy, College of Medicine, Riyadh, Ksa, [2]Assistant Professor, Department of Internal Medicine, Faculty of Medicine, Jazan University, Ksa

ABSTRACT

Polycythaemia Vera or erythrocytosisis a medical condition with high concentration of red blood cells. The thicker blood is less able to travel through blood vessels and organs. Most symptoms of polycythaemia are related tothis sluggish blood flow. Moderate symptoms of polycythaemia include headache, blurredvision, red skin, tiredness, elevated blood pressure, dizziness, abdominal discomfort, bleeding problems, gout and itchy skin although more severe medical events like vas-occlusion, thrombosis and strokes may occur. This case reports a 50 year old female with an unusual presentation of polycythemia vera in the form of abrupt onset 'one-day-old' history of massive hematemesis with otherwise unremarkable physical exam except caput medusa around umblicus. A diagnosis of Polythythaemiavera complicated by portal vein thrombosis induced portal hypertension was finally made.Patients with polycythemia vera are at high risk of vaso-occlusive events. While the etiology of events in polycythemic patients is likely to be multifactorial, hemodilution is potentially beneficial. Attending clinicians should be well aware of the unlikely associations and squeal of thrombotic events in polycythemia vera like portal venous occlusion and hypertension.

Keywords: Polycythemia vera, Portal vein, Hematemesis

INTRODUCTION

Polycythemia Vera (PV) is a disorder in which the bone marrow makes too many red blood cells albeit it may also result in an overproduction of white blood cells and platelets.[1] Many health concerns associated with PV are caused by the blood being thicker and sluggish to flow. It is more common in post middle age and the elderly. Presentation of PV may be symptomatic or asymptomatic. Common symptoms include headache, dizziness, itching (prurities), burning pain and redness of face, hands or feet, gout and abdominal discomfort. Patients with PV are prone to the development of blood clots and vaso-occlusive events.[2]

CASE REPORT

A 50-year-old female was admitted to King Fahad hospital,Jazan,KSA because of a one-day history of massive hematemesis. She was quite well till the day before admission when she suddenly vomited blood massively. She had no melena or bleeding from other sites. She gave no history of dyspepsia or weight loss. She denied any previous history of jaundice or Schistosomiasis. She wasn't on long-term medications except for interrupted use of paracetamol for headaches, which tended to occur frequently. At time of arrival to the hospital she was hemodynamically unstable with a BP of 90/70, a pulse rate of 110 b/min. She had cold extremities but no peripheral stigmata of chronic liver disease. Her abdominal examination revealed dilated veins around the umbilicus (Caput medusae), Splenomegaly (10 cm), liver span of 10 cm and mild ascites. The rest of her physical examination was unremarkable. She was immediately resuscitated with intra venous fluids and blood, then an urgent upper GI endoscopy was performed. It revealed grade 3 esophageal varices. They were successfully sclerosed. Her CBC revealed Hb of 16 gm, PCV of 60%,RBC: ESR of 10 mm/hr and normal platelets count. Her liver and renal function tests were within normal limits. Coagulation profile was normal. Bone marrow revealed erythroid hyperplasia. Abdominal ultrasonography reported portal vein thrombosis (Figure 1). So a diagnosis of PV complicated by portal vein thrombosis causing portal hypertension was finally made. Low dose aspirin was prescribed to prevent microvascular thrombotic complications of thrombocythaemia in remission after a routine phlebotomy and routine anticoagulant therapy regime. It is unusual for PV to present with acute portal vein thrombosis. In the absence of non-cirrhotic

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Corresponding Author:
Dr Tabinda Hasan, Assistant Professor, Department of Anatomy, College of Medicine, Riyadh, Ksa, E-mail: drtabindahasan@gmail.com

non-malignant extra hepatic portal vein thrombosis, myeloproliferative disorders like PV should always be considered. We hope that this case reports serves as a reminder of the association of portal venous events and PV in unexplained hematemesis cases.

DISCUSSION

PV is a clonal disorder arising in a multipotent hematopoietic progenitor cell that causes accumulation of morphologically normal red cells, white cells, platelets, and their progenitors in the absence of a definable stimulus. The increased hematocrit of PV is the main determinant of heightened blood viscosity. As the viscosity increases, vascular and organ blood flow decreases.[3]

Although caused by a genetic fault, PV is not usually inherited, with most cases appearing in later life(55-60yrs). While mild cases of PV go unmarked, the clinical course of PV is marked by a high incidence of thrombotic complications; especially MI and strokes. Fibrotic and leukaemic disease transformations are additional causes of morbidity and mortality. Most vaso-occlusive events in polycythemic patients are due to propagation of a local thrombus (Figure 2). Increasing age and a history of vascular events have consistently proven to be independent predictors of thrombosis in patients with PV.[4]

Polycythaemia can be diagnosed by carrying out blood tests to check the red blood cell count and haematocrit level. Elevated levels are suggestive of polycythaemia. Treatment for polycythaemia aims to prevent symptoms and complications, particularly blood clots. These include vene-section, systemic medications to reduce red blood cell production like hydroxycarbamide and interferons. Healthy lifestyle changes like weight reduction and quitting smoking are also advocated. Management of acute thrombotic events in polycythemia is vital; the American Heart Association guidelines stress on the immense value of hemodilution.[5,6]

Genetic Basis of PV

In 2005, a chromosomal clue to the molecular basis of PV was elucidated as a somatic, dominant, gain-of-function mutation in a region of thepseudokinase domain of the JAK2 (Janus kinase) gene. The JAK2 V617F mutation was described as a base pair transversion that results in a single amino acid substitution of phenylalanine for valine on the short arm of chromosome 9 The JAK2 V617F mutation on chromosome 9p24 increases the proliferative capacity of cells in all erythropoietin-independent erythroid colonies. Not all patients with PV demonstrate a loss of heterozygosity at the 9p locus; rather, the 9p locus merely serves to identify the location of JAK2 allele, and patients with polycythemia may be heterozygous or homozygous

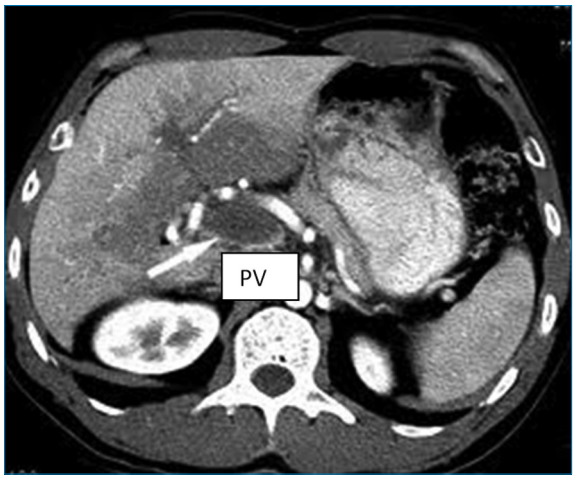

Figure 1: CT scan showing portal vein thrombosis

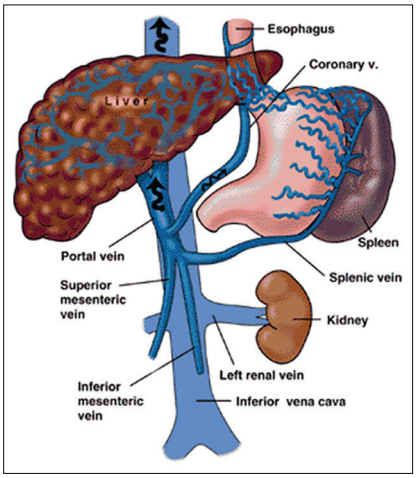

Figure 2: Local vessel wall thrombus propagation in hyper-coaguable states Courtesy:Giyabradiology available at: http://giyabradiology.blogspot.com/2011/05/portal-vein-inferior-vena-cava.html

for the JAK2 V617F mutation. It is the JAK2 V617F mutation, however, regardless of its homozygous or heterozygous presentation on a chromosomal level, that is seen in almost all polycythemia verapatients (Over 95%) and the JAK2 mutation, therefore, is virtually pathogenomic for polycythemia vera. Owing to this genetic basis, JAK2 V617F mutation has gained popularity as a noninvasive diagnostic tool in PV patients.[4]

Pathophysiologic Role of JAK2 in the Mechanism, Manifestations, and Management of the Disease

JAK2 functions as a cytoplasm tyrosine kinase which transduces signals from hematopoietic growth factors in both normal and euplastic multipotent hematopoietic progenitor cells. Because of the characteristic JAK2 mutation occuring in hematopoietic progenitor cells, the circulating erythrocytes, granulocytes, and platelets that are derived from these euplastic precursors also harbor the mutation. This results in a panmyelosis, with marked qualitative and quantitative dysfunction that affects all

the three lineages. PV, is classically characterized by neoplastic erythroid cells that proliferate in the absence of erythropoietin because of repetitive signaling by the mutated JAK2 protein. While this results in an increased red blood cell number and mass (that are part of the diagnostic criteria for PV), this hyperviscosity is not the 'sole' mechanism of the hypercoagulable state observed in the disease. Portal and hepatic venous thrombosis are most often the result of 'more than one' thrombotic risk factor and are not due to single, isolated events; thrombophilic genotypes or deficient functional natural anticoagulants being equally prevalent among PV patients with arterial disease. As a consequence of mutated JAK2 function, there is generalized hypersensitivity to cytokines, with over-expression of pro-coagulant factors and adhesion molecules at the vascular wall. Specifically, there is activation of hemostasis, with increased expression of platelet-associated tissue factor microparticles and resultant increased formation of platelet-neutrophil aggregates. This results in platelet hypersensitivity to these prothrombotic signals, as they undergo spontaneous activation, product secretion like thromboxane A2, and aggregation mediated by von Willebrand factor. Platelet plugs then transiently occlude the microvascular circulation. It is the presence of these defective circulating platelets which also explains the bleeding diathesis that is another, seemingly paradoxical, characteristic of the disease. While increased whole blood viscosity due to high hematocrit certainly contributes to hypercoagulability of PV, phlebotomy reduces but does not totally eliminate the increased risk for thromboembolism. An especially intriguing fact about myeloproliferative disorders like PV, is that the same mutation that defines the neoplastic, clonal proliferation of tri-lineage myeloid precursors in the bone marrow and their descendants in the blood is also responsible for the hypercoagulable state of the disease. Thus, JAK2 mutation of PV not only defines the molecular basis for the disease, but is also responsible for its sequel, like increased erythrocyte number and mass, hypercoagulability, and prutitis, as well as its response to hydroxyurea(HU); the current mainstay of therapy.

Discussion of Management of Acute Portal Venous Thrombosis in PV

The mainstay of treatment in acute cases of portal venous thrombosis should be to recanalize the obstructed veins and prevent extension of the thrombus. The current recommendation is oral anticoagulant therapy for at least 3 months aiming to keep level INR of 2.0-3.0.[7] Special attention to clinical and laboratory monitoring is required because of potentially greater bleeding risk and unpredictable drug influences in myeloproliferative disorder patients. Life-long warfarin prophylaxis has been advocated for patients with abdominal venous thrombosis.[8] No study has shown any critical benefit of beta blocker or endoscopic therapy for oesophageal varices in portal venous thrombosis patients, so only routine sclerosis was recommended in this patient.

Phlebotomy is the mainstay of treatment provided the patient can tolerate with a target haematocrit of 0.45.[9] Low dose aspirin reduces the risk of thrombotic events and much lower incidences of cardiovascular death, myocardial infarction, stroke, and major venous thromboembolism have been observed.[10] The recommended daily dose is 75 mg. HU is the most widely used cytoreductive drug, it reduces both haematocrit and platelet count which makes it the drug of choice in high-risk patients.[11] The initial dose of HU around 15to 20 mg/kg/day and the maintenance dose should aim to keep the haematocrit at response levels without reducing WBC count values <3 x 109/L8. In one study it was found that HU alone did not enhance the risk of leukemia in comparison to patients treated with phlebotomy only. Simultaneously, the risk was significantly increased by exposure to P32, busulfan, or pipobroman.[12] Therefore, appropriate cytoreduction with the goal to optimize the control of the blood cell counts is recommended in all patients with acute vascular events.[13]

Maintenance of INR within recommended levels and a high degree of motivation for continuing treatment is required in PV patients because of their inherent bleeding tendency and thrombotic complications.

Although unusual, acute portal venous thrombosis related events like portal hypertension and massive hematemesis may be an initial presentation of PV in previously symptomless patients. All clinicians should be aware of such uncommon associations of PV, caused by heightened viscosity led vascular thrombotic events, especially in cases with bleeding diathesis. A thorough patient examination and watching out blood profile and the 'tell-tale' caput medusa sign can facilitate life saving early intervention; particularly in sudden onset severe bleeding cases.

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