Case Report

Portal Vein Thrombosis in Polycythaemia Vera: A Case Report

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ABSTRACT

Portal vein thrombosis, commonly associated with cirrhosis of liver and thrombophilia, is one of the rare causes of sudden severe abdominal pain. In the absence of non-cirrhotic non-malignant extra hepatic portal vein thrombosis (EPVT), myeloproliferative disease (MPD) should always be considered. We describe a case of Polycythaemia Vera (PV) presenting with severe abdominal pain due to portal vein thrombosis. The patient was prescribed life-long warfarin, beta adrenergic blocker and aspirin. Due to uncontrolled platelet and white blood cell count he was later prescribed cytoreductive therapy.

Key word: Polycythaemia, portal vein thrombosis

Case Report:

A 26 year old youngman presented with the complaints of sudden severe abdominal pain for 4 days in August, 2007. It was dull aching in nature, associated with nausea and vomiting not accompanied by haematemesis and melaena. He was afebrile and gave no history of dark urine,headache, seizure, loss of consciousness, generalized itching or erythromelalgia.

Physical examination revealed congested lower palpebral conjunctiva without facial plethora. He was non icteric. Spleen was palpable 10 cm from left costal margin in non-tender soft abdomen. Ascites was absent. Initial investigations and treatment with anticoagulation was done in the dept. of Gastroenterology in collaboration with the dept of Haematology and Vascular Surgery.

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At presentation lab investigation revealed Hb(Haemoglobn) 16.5g/dl, WBC 11.0 x109/L, ESR 10 mm1st hour, Hct(Haematocrit) 0.51, Platelet 350 x109/L, serum bilirubin 1.8 g/dl, serum total protein 8.1 g/dl, and albumin 4.5g/dl.

The first USG (Ultrasongogram) done on September 9, 2007 (Fig-1) showed liver with homogenous echo texture with increased periportal echogenecity and echogenic structures noted within the portal vein along with cavernous formation. Duplex scan confirmed the echogenic structure to be thrombus in the lumen of main portal trunk causing partial obliteration (Fig-2). Mean velocity within the cavernous was 30.6 cm/sec. Thrombus was still present within the portal vein after anticoagulation(Fig-3), however, cavernous velocity was increased (35.6 cm/sec). Endoscopy upper GIT showed grade I esophageal varices with duodenal erosion. Later on he was treated with warfarin 5 mg and Propranolol 20 mg Daily. Two months later a follow up Color Doppler showed re-canalization of portal vein, a normal hepatic vein flow and development of collateral vessels in hilar and peripancreatic region along with moderate splenomegaly (18.5 cm).

Differential diagnoses:

The diagnosis of acute EPVT was confirmed by USG. Causes of abdominal pain like appendicitis, pancreatitis, cholecystitis, cholangitis and inflammatory bowel diseases were excluded by history, examination and USG. Liver function tests including the viral markers and renal function were also normal. Amongst other causes of systemic prothrombotic states were inherited thrombophilia, MPD, so our differential diagnoses were inherited thrombophilia and MPD.

Coagulation screening test were done PT(Prothrombin time) 12.4s, APTT(activated partial thromboplastin time) 35.5s, TT (Thrombin time) 12s, Fibrinogen 200mg/dl were found to be normal. ATIII (Anti-thrombin III, 118.6%) and APCR (Activated protein C resistance, 2.45) were found negative, protein C (121.7%) and protein S (76.4%) were also normal. Ham's test, sucrose lysis test and sickle test were negative (Table-I).

Arterial blood gas analysis was normal. Bone marrow aspiration study revealed panmyelosis with predominant

erythroid and megakaryocytic hyperplasia. Finally, we requested JAK2 kinase mutation study and FISH for bcr-abl in a reference laboratory abroad. The patient was found to be positive for 2343G-T mutation in JAK 2 gene resulting in amino acid change Valine in 617 phenyal alanine. FISH for bcr-abl was negative.

Discussion of Pathology:

Polycythaemia Vera is a clonal haemopoietic chronic myeloproliferative stem cell disorder involving hyperplasia of all three major cell lineages. The main pathological feature is expansion of total red cell mass with independent of erythropoietin, elevation in platelets and neutrophils[17,18]. The median age of onset is 55-60 years[1] with cases under the age of 20 being very rare [18]. The JAK2 V617F mutation increasing the proliferative capacity of cells is present in all erythropoietin-independent erythroid colonies

Table 1 : Molecular analysis for inherited thrombophilia results were as follows:

Mutations analyses	Patient DNA	Result
Factor V 1691	Factor V 1691G/G	Normal
Factor II 20210	Factor II 20210 G/G	Normal
MTHFR677	MTHFR677C/C	Normal

Clinical diagnosis:
Polycythaemia Vera with portal vein thrombosis and portal hypertension

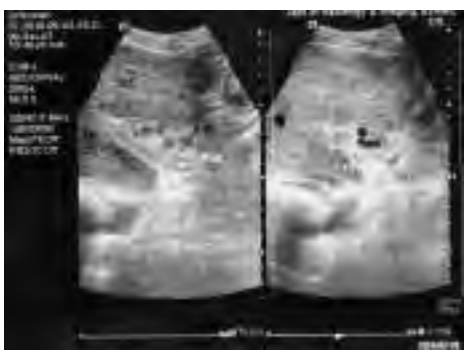

Figure 1: Initial sonographic finding

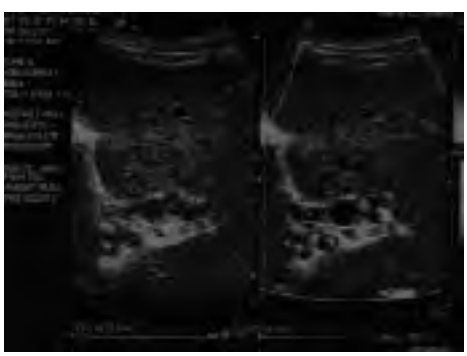

Figure 2: Color Doppler portal venous system

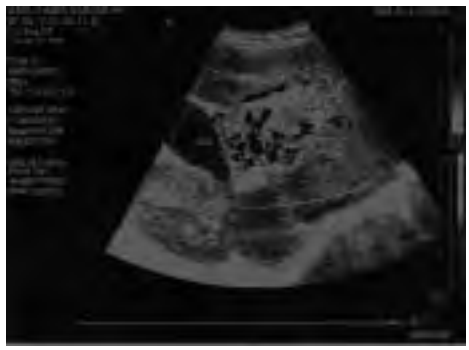

Figure 3: Follow Up Doppler after anticoagulation

in PV. The mutation is present in 90-95 % of PV patients and in approximately 50 percent of Essential Thrombocytosis and IMF (Idiopathic Myelofibrosis) patients[1]. Mutation in the gene for Janus Kinase 2 (JAK2V617F) on chromosome 9p24 (4-7) has gained popularity as a noninvasive diagnostic tool[2-4]. The major symptoms related to hypertension and vascular abnormalities are caused by the increased red cell mass. An episode of venous or arterial thrombosis such as deep vein thrombosis, MI or stroke may be the first manifestation in about 25% cases. Mesenteric, hepato-portal or splenic vein thrombosis should always raise suspicion of PV as a possible cause[18].

WHO definition of absolute erythrocytosis as haemoglobin levels >18.5 g/dL (haematocrit > 55.5%) in a man or >16.5 g/dL (haematocrit > 49.5%) in a woman has been questioned by several authorities for its low efficiency (It identified absolute erythrocytosis in only 35% of male PV patients and 63% of the females) and high false positive rate (14% in male and 35% in female)[5]. The clinical course of polycythaemia vera (PV) is marked by a high incidence of thrombotic complications; fibrotic and leukaemic disease transformations are additional causes of morbidity and mortality[6]. Increasing age and a history of vascular events have consistently proven to be independent predictors of thrombosis in patients with PV[7]. Leukocytosis has been identified as risk factor for thrombotic events specially MI (Myocardial infarction)[7-8]. No study to date has demonstrated a significant correlation between platelet number or function and thrombosis[9-10].

Discussion of management:

Patient treated with aspirin 75mg, warfarin and propanolol The patient was treated with aspirin 75mg, warfarin and propanolol and was advised monthly follow up. At the first follow up visit, lab values were Hb 15 g/dl, Hct 0.45, WBC 14 x109/ L, Platelet 500 x109/ L and INR 2.0. Since then he had been under regular follow up and the parameters were within control. A CBC on May, 2008, showed increased number of basophils (5%), nucleated red cells and platelet 700 x109/ L .In next visit platelet and WBC count continued

to rise with persistent basophilia and nucleated red cells in film. At that time he complained of erythromelalgia, redness of sole and palm and intense itching. A cyto-reductive drug, Hydroxyurea (HU) 500 mg twice daily was added, dose of Warfarin increased to 6.25 mg daily and follow up was recommended after two weeks. Later on total count came down to 11 x109/ L, platelet count to 300 x109/ L and Hct 0.39. He was kept on HU at same dose for another 2 weeks and then it was gradually tapered to a maintenance dose of 500mg daily. Other previous medications were continued at same doses during that period.

In treating acute EPVT, our target is recanalizing the obstructed veins and preventing extension of the thrombus. The current recommendation is oral anticoagulation for at least 3 months aiming to keep level INR of 2.0-3.0[11]. Special attention to clinical and laboratory monitoring is needed because of potentially greater bleeding risk and unpredictable drug influences in MPD patients[12]. Life-long warfarin prophylaxis has been advocated for patients with abdominal venous thrombosis[13]. No study showed critical benefit of beta blocker or endoscopic therapy for oesophageal varices in EPVT patients, however, we recommended this patient beta blocker.

Phlebotomy is the mainstay of treatment provided the patient can tolerate with a target haematocrit of 0.45[14]. Low dose aspirin reduces the risk of thrombotic events as such lower incidences of cardiovascular death, myocardial infarction, stroke, and major venous thromboembolism are observed[6]. The recommended daily dose is 75 mg[19].

HU, the most widely used cytoreductive drug, reduces both haematocrit and platelet count which makes it the drug of choice in high-risk patients[15]. The initial dose of HU is 15 to 20 mg/kg/day and maintenance dose should be administered to keep 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 with patients treated with phlebotomy only. During the same period, the risk was significantly increased by exposure to P^{32}, busulfan, or pipobroman Appropriate cytoreduction with the goal to optimize the control of the blood cell counts is recommended in all patients with acute vascular events[16].

USG after on June 30, 2008 (While on regular warfarin and propranolol therapy) showed persistent splenomegaly (about 17 cm) and persistence of periportal echogenic shadow and also collateral channel around porta hepatis. Maintenance of INR was maintained within the recommended level with some degree of difficulty because of the inherent bleeding tendency associated with Polycythaemia Patient also needed a high degree of motivation for continuing treatment.

References:

1. Tefferi, A., JAK2 mutations in polycythemia vera--molecular mechanisms and clinical applications. N Engl J Med, 2007;356:444-5.

2. Gangat, N., et al., Cytogenetic studies at diagnosis in polycythemia vera: clinical and JAK2V617F allele burden correlates. Eur J Haematol, 2008;80:197-200.

3. Tefferi, A., A refined diagnostic algorithm for polycythemia vera that incorporates mutation screening for JAK2(V617F). Curr Hematol Malig Rep, 2006;1:81-6.

4. Tefferi, A., Classification, diagnosis and management of myeloproliferative disorders in the JAK2V617F era. Hematology Am Soc Hematol Educ Program, 2006;240-5.

5. Spivak LJ, a.S.T.B.-. The revised World Health Organization diagnostic criteria for polycythaemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. Blood, 2008;112:231-239.

6. Finazzi, G. and T. Barbui, How I treat patients with polycythemia vera. Blood, 2007;109:5104-11.

7. Landolfi, R., et al., Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood, 2007;109:2446-52.

8. Gangat, N., et al., Leucocytosis in polycythaemia vera predicts both inferior survival and leukaemic transformation. Br J Haematol, 2007;138:354-8.

9. Pearson TC, M.M., Westwood N, Green RA., A Polycythaemia Vera Update:Diagnosis, Pathobiology and Treatment. Hematology, 2000;51-68.

10. Levine RL, W.G., Role of JAK-STAT Signaling in the Pathogenesis of Myeloproliferative Disorders. Hematology, 2006;233-239.

11. Spaander, V.M., H.R. van Buuren, and H.L. Janssen, Review article: The management of non-cirrhotic non-malignant portal vein thrombosis and concurrent portal hypertension in adults. Aliment Pharmacol Ther, 2007;26: 203-9.

12. Elliott, M.A. and A. Tefferi, Pathogenesis and management of bleeding in essential thrombocythemia and polycythemia vera. Curr Hematol Rep, 2004;3:344-51.

13. Condat, B., et al., Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology, 2001;120:490-7.

14. Di Nisio, M., et al., The haematocrit and platelet target in polycythemia vera. Br J Haematol, 2007;136: 249-59.

15. Dingli, D. and A. Tefferi, Hydroxyurea: The drug of choice for polycythemia vera and essential thrombocythemia. Curr Hematol Malig Rep, 2006;1:69-74.

16. McMullin, M.F., et al., Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol, 2005;130:174-95.

17. Vassiliou G, Green RA, Myeloproliferative disorders. In: Hoffbrand AV, Catovsky D, Tuddenham GD (Eds). Postgraduate Haematology. 5th edition. Blackwell publishing, Oxford, London, 2005;761-782.

18. Pierre R, Vardiman JW, Imbert M, Brunning RD,Thiele J, Flandrin G.Polycythaemia Vera. In: World Health Organization classification of tumors: pathology and genetics of tumors of haematopoietic and lymphoid tissues,2001;32-34.

19. Guidelines for the diagnosis and treatment of patients with Polycythaemia Vera, Essential thrombocythemia and Idiopathic myelofibrosis. Nordic MPD study Group. http://www.nordicmpd.org/guidelines.html