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Hyperviscosity: A Rare Cause of Portal Hypertension in Polycythemia Vera

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1. Abstract

A 36-year-old man with medical history of JAK2 positive Polycythemia Vera presented to our institution with a six-week history of progressive increase in abdominal circumference, coluria, and abnormal liver chemistry. He was diagnosed with non-cirrhotic portal hypertension due to hyper viscosity without thrombosis. A trans jugular intrahepatic portosystemic shunt was placed.

2. Introduction

Polycythemia Vera (PV) is a BCR-ABL1 negative Myeloproliferative Neoplasm (MPN) characterized by the presence of an elevated mature red blood cell mass. Thrombotic events in atypical locations such as Splanchnic Vein Thrombosis (SVT) are classically associated with MPN. We present a case of portal hypertension due to hyper viscosity without SVT in a man with PV.

3. Case Report

A 36-year-old man presented to our institution with a six-week history of progressive increase in abdominal circumference, coluria, and abnormal liver chemistry. Past medical history included JAK2 positive Polycythemia Vera diagnosed 3 years before consultation treated with acetylsalicylic acid 100 mg daily and regular exchange transfusions. He reported no complications due to PV. Physical examination revealed jaundice, grade II non-tender ascites, and caput-medusae, with no other signs of chronic hepatopathy stigmata. Blood tests revealed polyglobulia, hypoalbuminemia, hyperbilirubinemia with elevated alkaline phosphatase and gamma-glutamyl transpeptidase, normal transaminases, and delayed prothrombin time. Serology against viral hepatitis revealed antibodies against hepatitis B virus S antigen (HBVs-Ab) owing to vaccination. TORCH Screen was positive with IgG against Rubella virus and CMV (Table 1). An abdominal ultrasound was performed and showed diffuse hepatopathy, gallstones, hepatosplenomegaly, and ascites. Abdominal CT Scan with IV contrast exhibited diffuse fibronodular hepatopathy, splenomegaly, ascites, gallstones, and splenic vein thrombosis. Portography was negative for thrombosis, and low flow was observed on the splenic and portal vein suggesting hyper viscosity (Figure 1).

Cytologic study of ascites was negative for malignancy and microorganisms. Liver biopsy revealed edema, diffuse microhemorrhages, and lobular fibrosis of approximately 40% of the examined tissue due to ischemic injury. These findings were compatible with histopathological changes due to hyperviscosity syndrome and no evidence of cirrhosis (Figure 2).

He was referred to a third-level institution for hepatology and hematology follow up, and a Transjugular Intrahepatic Portosystemic Shunt (TIPS) was placed for symptom relief (Figure 4). Prior to TIPS placement an echocardiogram was performed which showed normal ventricular function, low probability for pulmonary hypertension and minimal pericardial effusion. TIPS was performed via transhepatic puncture because of difficulties to reach suprahepatic veins from the jugular access, and a 10x80x20 mm covered stent was placed (Gore® Viatorr®). No thrombosis nor stenosis were seen during the procedure. Hepatic venous pressure gradient measurement was not technically possible. Patient was discharged 24

hours after the procedure without any complications and was prescribed apixaban and hydroxyurea. After three months follow up, the patient was on minimal doses of furosemide (20 mg/d) and spironolactone (50 mg/d) with no edema or ascites.

Table 1: Laboratory Data

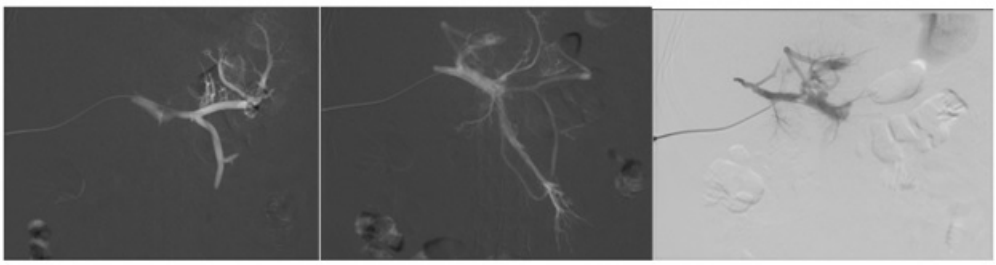
Hematology	Blood chemistry	Coagulation	Serology
WBC 7.2 10^3/uL	AST 51 U/L	PT 21s	IgG Rubella (+)
Hb 16.9 g/dL	ALT 18 U/L	INR 1.66	IgM CMV (-)
Hct 53.1%	AP 251 U/L	aPTT 32.7s	IgG CMV (+)
MCV 78 fL	GGT 186 U/L	Fibr 321 mg/dL	IgM CMV (-)
MCH 31 Pg	Total Bil 3.8 mg/dL		IgG Toxoplasma (-)
PLT 331 10^3/uL	Direct Bil 2.7 mg/dL		IgM Toxoplasma (-)
	Alb 2.1 g/dL		HSV1-Ab (-)
	LDH 268 U/L		HSV2-Ab (-)
	BUN 36 mg/dL		HBs-Ab 67.8 mUI/mL
	Cr 0.7 mg/dL		HBs-Ag (-)
	UA 4 mg/dL		HBe-Ab (-)
	Na 127 mmol/L		HBe-Ag (-)
	K 4.06 mmol/L		HBc-Ab (-)
	Cl 104 mmol/L		HCV-Ab (-)
	Ca 9.6 mg/dL		HAV-Ab (-)
	P 3.8 mg/dL		
	Mg 2 mg/dL		

WBC: white blood cells. Hb: hemoglobin. Hct: hematocrit. MCV: mean corpuscular volume. MCH: mean hemoglobin concentration. PLT: platelets. AST: Aspartate transaminase. ALT: Alanine transaminase, AP: alkaline phosphatase. GGT: gamma-glutamyl transpeptidase. Alb: Albumin. LDH: lactate dehydrogenase-. BUN: blood urea nitrogen. Cr: creatinine. UA: uric acid. PT: prothrombin time. INR: international normalized ratio. aPTT: activated partial thromboplastin time. Fibr: fibrinoge. IgG: G immunoglobulin. IgM: M immunoglobulin. CMV: citomegalovirus. HSV1: herpes-simplex 1 virus. HSV2: herpes simplex 2 virus. Ab: antibodies. Ag: antigen. HBs-Ag Hepatitis B Virus S antigen. HBs-Ab: antibodies against hepatitis B Virus S antigen. HBe-Ab: antibodies against hepatitis B Virus E antigen. HBe-Ag: hepatitis B Virus E antigen. HBc-Ab: antibodies against hepatitis B Virus C antigen. HCV: hepatitis C virus. HAV: hepatitis A virus.

Table 2: Ascites cytochemical analysis

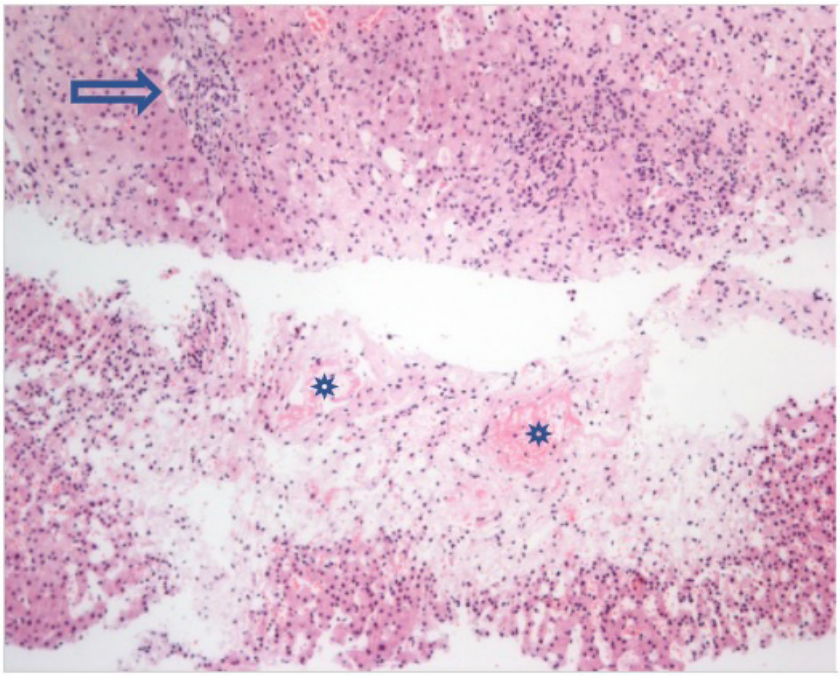
Color	Yellow
Density	1.018
pH	7
Erythrocytes	10000 cells/mm3
Leucocytes	140 cells/mm3
PMN	34%
Mon	66%
LDH	22 U/L
Glucose	97.5 mg/dL
Proteins	0.4 g/dL

PMN: polymorphonuclears. Mon: monocytes. LDH: lactate dehydrogenase.



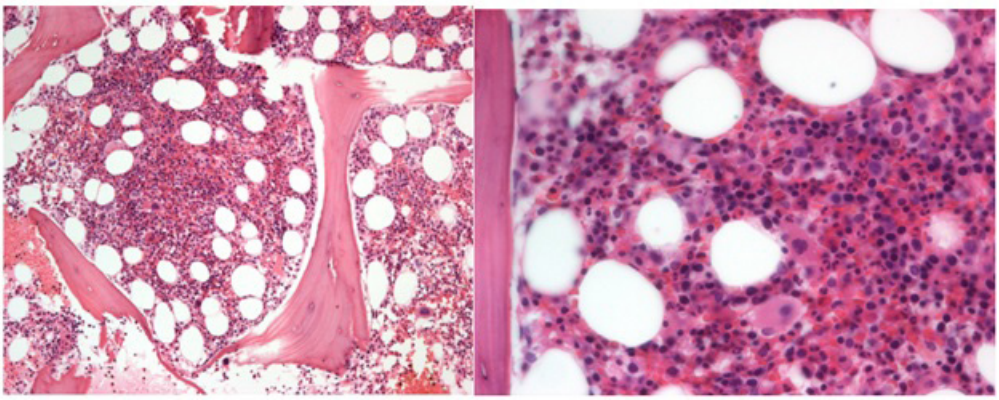
Portography showed no thrombi in the portal and splenic veins.

Figure 1: Portography



Congestive central veins (stars) surrounded by clear space of parenchymal collapse. Portal triad (arrow) with scarce inflammatory infiltrate. Sinusoidal dilatation in zone II is also evidente (HE 40X).

Figure 2: Liver biopsy



Hypercellular bone marrow with erythroid precursors increase (HE X40). Normoblast nuclear variation and hypolobulated megakaryocytes admixed with clusters of granulocyte precursors are observed at high power (X100).

Figure 3: Bone Marrow biopsy

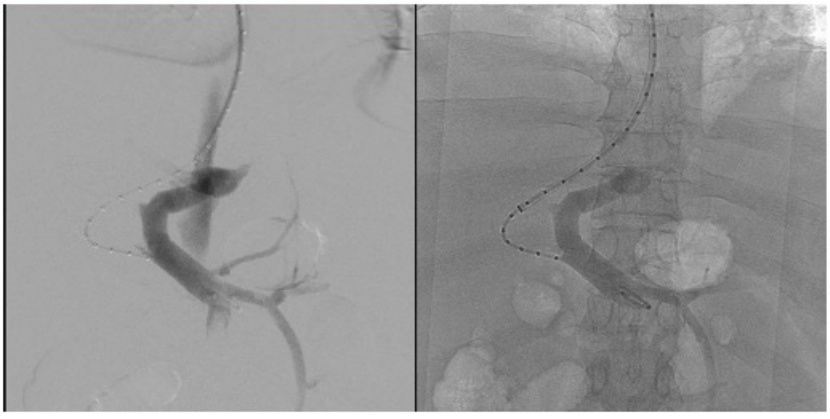


Figure 4: TIPS

4. Discussion

Non Cirrhotic Portal Hypertension (NCPH) is classified into prehepatic, intrahepatic and posthepatic. It is a heterogeneous group of liver disorders of vascular origin, leading to Portal Hypertension (PHT) with near normal Hepatic Venous Pressure Gradient (HVPG) and significantly elevated portal vein pressure [1]. One common NCPH cause is portal vein thrombosis, which may be seen in patients with chronic myeloid leukemia, deficiency of natural anticoagulant proteins, hereditary thrombophilias, and Polycythemia Vera (PV) [2,3]. Mechanisms involved in the hypercoagulable state associated with PV are not fully understood, but abnormalities in blood viscosity, platelets, leukocytes, fibrinolytic activity and endothelial damage have been implicated [4].

Portal thrombosis in the acute phase commonly presents as abdominal pain, nausea or vomiting, whereas splenomegalia, ascites and gastrointestinal bleeding are seen in chronic cases. However, our patient had no evidence of thrombi as revealed by portography, considered the gold standard for diagnosis. In the absence of major vascular thrombosis, a presinusoidal component could explain an increased resistance to the venous flow at the level of the portal venules. There may be obstruction secondary to extra medullary hematopoiesis within the sinusoids [5]. Also, the findings in an autopsy series of 145 patients with PHT secondary to polycythemia vera or idiopathic myelofibrosis suggest that portal venule obstruction could be the consequence of microthrombosis [6]. Although no alterations were found at this level in the liver biopsies, the small size of the obtained specimens cannot exclude anatomical abnormalities. Nonetheless, the contributory role of the slow blood flow in worsening the portal hypertension may be significant, which in turn can be explained by increased viscosity.

Polycythemia vera is a well-known risk factor for increased whole blood viscosity, which has the characteristics of a non-Newtonian fluid; it depends on blood flow and blood cell composition [7]. On the one hand, the viscosity of whole blood increases as the red cell count and hematocrit increases [8]. When it exceeds 50%, there is a rapid increase in viscosity. It increases three-fold between a hematocrit of 50% and 80%. If red cells were not deformable, blood would gel at a hematocrit above 70, but blood continues to flow at high hematocrit levels because red cells are highly deformable [9]. Whole-blood viscosity, therefore, depends on hematocrit, the reversible aggregation of red cells, the mechanical properties of red cells, as well as the viscosity of plasma, which is affected by fibrinogen, albumin, and globulin levels [7]. On the other hand, whole blood viscosity also depends on factors that cause red cells to aggregate. At low shear rates, red cells are aggregated; the major factor controlling aggregation is cell-to-cell adhesion, known as the Z potential. Patients with PV have a change in viscosity three times higher at low shear rates, compared to healthy individuals [10].

Typically, hyperviscosity manifests with neurological symptoms, including headache, vertigo, tinnitus, dizziness, altered mental status and confusion. The classic hyperviscosity syndrome triad is mucosal bleeding, visual abnormalities, and neurological abnormalities. Our patient mentioned none of these complaints; however, the pathophysiology behind those symptoms is decreased perfusion and microhemorrhages, as seen on the patient's liver biopsy [10]. Burak et al reported a prevalence of PH of 13.8% amongst 29 patients with Ph negative MPN as a result of the massively increased splenoportal blood flow and the decreased hepatic vascular compliance or hepatic venous thrombosis. However, in their case series, only 2 out of 4 patients with PH had thrombosis in intra-abdominal large veins [11].

In conclusion, we present a patient with ascites due to NCPH caused by hyperviscosity in splanchnic circulation.To our knowledge, there are no published cases of NCPH due to PV without thrombosis. It is important to keep in mind that histopathologic analysis was negative for cirrhosis, which could have been another explanation of the PHT. This may represent an atypical manifestation of end-organ damage due to hyperviscosity.

Informed patient's consent was obtained for submission of this case report.

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