Splanchnic venous thrombosis driven by a constitutively activated JAK2 V617F philadelphia-negative myeloproliferative neoplasm: a case report

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Abstract.

Introduction: Splanchnic venous thrombosis (SVT) has varied etiology with Philadelphia- negative myeloproliferative neoplasms (MPNs) being the most frequent underlying prothrombotic factor. Hematological indices often remain within normal range because of portal hypertension and its sequelae, causing diagnostic challenges. The high frequency of JAK2 mutation among patients with SVT reinforces the diagnostic utility of JAK2V617F testing.

Case report: We report a case of a 62-year-old black man with progressive abdominal swelling and features of decompensated chronic liver disease found to have SVT- portal vein thrombosis and how JAK2 V617F was useful in unmasking an underlying myeloproliferative neoplasm.

Conclusion: A high index of suspicion for an underlying prothrombotic factor is critical for patients presenting with thrombosis in unusual sites. This is useful in prognostic stratification and patient outcomes. JAK2 mutation screening is now part of the standard diagnostic workup in SVT.

Keywords: venous thrombosis, myeloproliferative neoplasm.

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Introduction

Splanchnic venous thrombosis (SVT) is a rare but life-threatening form of venous thrombosis and includes hepatic vein thrombosis (Budd-Chiari syndrome, BCS), portal vein thrombosis (PVT) and mesenteric vein thrombosis (MVT)[1]. Involvement of two or more abdominal vein segments usually occurs[2]. A thrombotic event in unusual sites such as intra-abdominal veins is cause for further evaluation of an underlying hypercoagulable state, both inherited and acquired thrombophilias. A more frequent association between Philadelphia-negative myeloproliferative neoplasms (MPNs) and SVT, in particular PVT and BCS, has been reported [3,4]. The MPNs are a related group of diseases with a common origin of an acquired stem cell defect leading to over proliferation of the myeloid series. Diagnosis of occult forms of MPNs may be difficult in the setting of SVT because of the near normal hematological indices resulting from portal hypertension. Nearly a decade ago, it was demonstrated that MPNs are connected by an acquired somatic mutation in the JAK2 gene, the JAK2 V617F mutation[5]. All patients with idiopathic intra-abdominal venous thrombosis should be screened for JAK2 V617F mutation in order to detect latent or occult MPNs[6].

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Case report

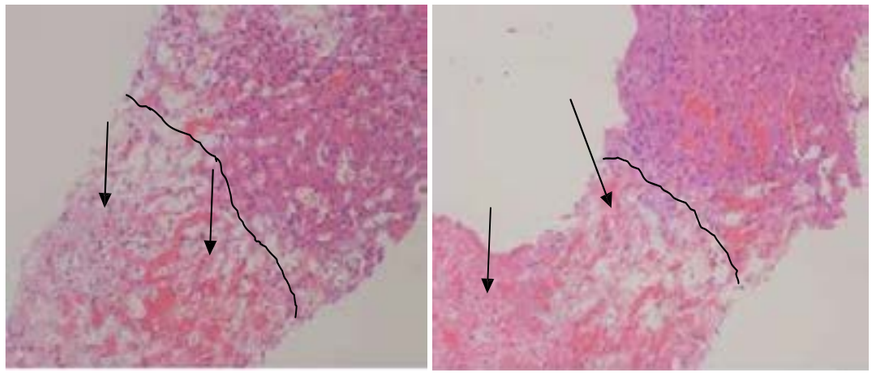
A 62-year-old black man of Tanzanian nationality growing up in the mountainous areas of Kilimanjaro presented to Mulago hospital with a 6 weeks history of progressive abdominal swelling associated with nausea and occasional non-projectile vomiting without hematemesis. Two weeks into admission, he developed pain in the right upper quadrant of the abdomen. He affirmed complaints of poor appetite and early satiety but normal bowel movements. He reported significant loss of weight, with associated low-grade fevers but no drenching sweats. His medical history was notable for systemic

hypertension two years prior to admission that was controlled on lisinopril and propranolol. He was also on low dose aspirin for the prevention of cerebrovascular events. He denied a history of liver disease, blood disorders or cancer. He was married with four children and was an agricultural researcher. He had never smoked cigarettes but drank 1-2 bottles of beer on weekends.

Initial physical evaluation revealed a jaundiced man, with mild pedal edema, hepatomegaly of 4 cm below the costal margin, and moderate ascites. A clinical diagnosis of decompensated liver disease with portal hypertension was made and a number of tests were done to exclude etiology and complications of liver disease. Laboratory tests revealed a marked transaminitis with; Alanine Aminotransferase at 1247U/L [30x ULN (upper limit of normal)], Aspartate Aminotransferase was 773U/L (20xULN), Total bilirubin 134µmol/L (7.8xULN), direct fraction was 66.2 µmol/L (19xULN) gamma glutamyl transferase was 365U/L (5.5x ULN). Renal function tests were normal as well as fasting lipids and glucose. Ascitic fluid analysis showed protein of 2.1g/dl, white cell count of 100cells/mm^3 with 80% lymphocytosis. Unfortunately, ascitic fluid albumin was not done making it impossible to determine serum-ascites albumin gradient (SAAG).

Complete blood count (CBC) on admission showed a total white cell count (WBC) of 9.82 x103/µL, haemoglobin of 18.5 g/dL, haematocrit of 54% and a rather high platelet count of 660 x103/µL. Serological markers for hepatitis B virus (HBV), hepatitis C virus (HCV) and the human immunodeficiency virus (HIV) were all negative. Tumor markers including Ca-19-9, CEA, total prostatic specific antigen (PSA) and alpha feto protein(AFP) were normal. Autoimmune screen was negative for Anti-nuclear factor and smooth muscle antibodies. S-ceruloplasmin at 33mg/dL, and prothrombin time were normal. Abdominal ultrasonography showed a splenomegaly and a hypodense lesion in the left lower lobe of the liver that revealed coagulative necrosis on histology consistent with hepatic infarction without evidence of malignancy.

Doppler ultrasound studies of the abdomen showed features of portal vein thrombosis with absent colour flow mapping in the portal veins but hepatic veins were not demonstrable. A subsequent doppler scan of both legs showed stagnation of flow in the deep calf veins and marked varicose veins bilaterally. The patient was initiated on anticoagulation with enoxaparin. A JAK2 V617F mutation assay was positive but without allele percentage. The patient while in hospital developed renal impairment, hepatic encephalopathy, and probable variceal hemorrhage leading to death.



Images of liver biopsy showing sharply demarcated areas of coagulative necrosis consistent with a defined infarct.
Diagnosis transmitted electronically from Cincinnati, Ohio, USA

Discussion

Based on the new-onset SVT combined with the finding of the JAK2 V617F mutation, our patient's condition was diagnosed as an underlying chronic MPN. The clinical presentation of SVT varies according to the extent, rapidity of obstruction and venous segment involved. Specifically looking at PVT, presentation may be asymptomatic, acute or chronic. Acute thrombosis is characterized by a sudden onset of abdominal pain without evidence of chronic portal hypertension (gastrointestinal bleeding, ascites, collateral portosystemic circulation or hypersplenism). Sonography may show hyperechoic material in the vessel lumen with distension of the portal veins and its tributaries.

Doppler imaging shows the absence of flow in part or all the lumen[7,8]. As demonstrated in the patient, chronic PVT is a late sequela of thrombosis usually defined by the presence of a portal cavernoma with features of portal hypertension. At imaging, a diagnosis of carvernoma is readily made by abdominal imaging with ultrasound, computed tomography or magnetic resonance scan which shows serpiginous structures while the main portal vein and or its branches are not visible[7, 9]. Many large-scale studies have been performed to study the underlying etiological factors in SVT. Both inherited and acquired thrombophilias are frequently observed in these patients. Philadelphia-negative MPNs are the most frequent underlying prothrombotic factor in BCS and PVT, with a reported prevalence of 30%-50% and 15%-30% respectively[7,10].

Markers of Philadelphia-negative MPNs such as endogenous erythrocyte colony formation by bone marrow and peripheral blood cells, JAK2 mutation and the increased mRNA expression of PRV-1 in polymorphonuclear neutrophils have gained strong popularity among clinicians because it represents significant improvement in prognostic stratification and therapeutic management of patients with SVT. Other etiological factors are paroxysmal nocturnal hemoglobinuria (PNH), autoimmune disorders, intra-abdominal inflammatory conditions, postoperative state, sickle cell anemia, anti-phospholipid syndrome, inherited hypercoagulable states (thrombophilias), including factor V Leiden, prothrombin G20210A mutation, protein C, protein S and anti-thrombin deficiencies.

Table 1 below shows the prevalence of thrombotic risk factors in a series of routinely investigated consecutive adult patients with non-tumorous and non-cirrhotic, acute and or
chronic PVT and BCS.

Risk Factors	PVT patients	BCS patients
Myeloproliferative disorders	30%-40%	40%-50%
Atypical	14%	25%-35%
Classical	17%	10%-25%
Antiphospholipid syndrome	6%-19%	4%-25%
Paroxysmal nocturnal hemoglobinuria	0%-2%	0%-4%
Behcet's disease	0% -31%	0%-33%
Factor V Leiden mutation	6%-32%	6%-32%
Factor II mutation	14%-40%	5%-7%
Protein C deficiency*	0%-26%	10%-30%
Protein S deficiency*	2%-30%	7%-20%
Antithrombin deficiency*	0%-26%	0%-23%
Plasminogen deficiency*	0%-6%	0%-4%
Recent pregnancy	6%-40%	6%-12%
Recent oral contraceptive use	12%	6%-60%
Hyperhomocysteinemia	12%-22%	37%
TT677 MTHFR genotype	11%-50%	12%-22%

*Regarded as preceding the development of PVT or BCS.
Adapted from American Association for the Study of Liver Diseases practice Guidelines, 2008

Diagnosis of MPN in the setting of SVT can however, be challenging owing to the near normal peripheral blood cell counts because of portal hypertension and its sequelae (splenomegaly, hemodilution and iron deficiency)[10].

The discovery of the JAK2 V617F gain-of-function mutation in 2005, found in 95% of patients with polycythemia vera (PV) and in 50%-60% of patients with essential thrombocythemia and myelofibrosis, represents a crucial advance in the diagnostic approach to MPNs in the setting of SVT[10,11]. The goals of therapy in patients with MPNs are to avoid thrombotic and bleeding complications and also to monitor for progression to acute leukemia and myelofibrosis. In a retrospective multivariate analysis of a large cohort including patients with chronic or acute PVT, it was found that anticoagulation therapy significantly decreased the risk of recurrent thrombosis without increasing the risk of gastrointestinal bleeding[12,13]. Recent case series on myeloproliferative neoplasms stratify care according to thrombotic risk into low risk (defined by absence of prior thrombosis and age <60 years), and high risk (defined by history of thrombosis, or age >60 years, poor compliance to phlebotomy, or progressive myeloproliferation, i.e. splenomegaly, leucocytosis and thrombocytosis). Although our patient had no history of thrombosis, he met the high risk criteria.

In polycythemia vera, low risk patients can be managed by phlebotomy to maintain hematocrit <0.45 and low-dose aspirin, while high risk patients require cytoreductive therapies with hydroxyurea and interferon-α. Busulfan can be used in elderly patients >75 years. For patients with essential thrombocythemia, anagrelide can be considered as second line therapy. Long term oral anticoagulation is useful in secondary prevention of thrombosis without significant increase in risk of major bleeding[14,15]. There is insufficient evidence in favour of interventional therapy and no consensus on the management of chronic portal vein obstruction. In case of worsening on medical therapy, patients should be considered for invasive procedures like angioplasty/stenting, transjugular intrahepatic portosystemic shunting and liver transplantation[16].

Hoekstra et al in their retrospective cohort study on long-term follow-up of patients with PVT and MPNs reported that mortality was primarily related to the underlying MPN and not to complications of portal hypertension[17]. Unfortunately our patient, though he had commenced anticoagulation and paracentesis, did not undergo phlebotomy or cytoreductive therapy. It was therefore impossible to assess the impact of these interventions on the patient's outcome.

Study limitations included the lack of thrombophilia screen, although results would have been difficult to interpret in the setting of liver failure and anticoagulation. Abdominal CT- angiography would have been useful in delineating vascular occlusion in BCS. Furthermore, sub- classification of the specific MPN with the help of additional tests including red cell mass determination was not done. Endoscopy was also not done because of the critical state of the patient.

Conclusion

In conclusion, a high index of suspicion for an underlying hypercoagulable state is required for patients presenting with thrombosis in unusual sites. This will lead to early definitive diagnosis, inform treatment and improve patient outcomes.

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