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Budd-Chiari Syndrome in a Patient with JAK-2 Mutation without Myeloproliferative Disorder

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Abstract

A 41-year-old woman presented with right upper quadrant abdominal pain, found to have a primary budd-chiari syndrome secondary to right hepatic vein thrombosis. Her thrombophilia workup revealed a JAK2 mutation is a setting of no signs of myeloproliferative disorders. JAK2V617F mutation could be a pro-coagulant to thrombosis even without myeloproliferative disorders.

count was normal. She has a negative hepatitis profile. Her pregnancy test was negative.

Abdominal ultrasound showed coarse appearing liver and moderate amount ascites. CT abdomen followed showed multiple hypoechoic hepatic vasculature lesions and right hepatic vein thrombosis. Liver venogram showed accessory right hepatic and right hepatic venogram demonstrates a spider-web appearance of intrahepatic venous collaterals, consistent with Budd-Chiari syndrome (BCS). The central aspect of the right hepatic vein is patent. Patient was started on heparin drip with bridge to Coumadin. She underwent a transjugular intrahepatic portosystemic shunt (TIPS) procedure which showed a severe portal hypertension (portosystemic gradient of 27 mmHg). TIPS creation from the middle hepatic vein to the right portal vein performed, with reduction of the portosystemic gradient to 8 mm Hg and was discharge home afterwards on Coumadin.

Her thrombophilia workup was positive for janus kinase 2 (JAK2) mutation (V617F) with 3.1% mutation. It was negative for factor 5 leiden mutation, prothrombin gene mutation, antiphospholipids antibodies, lupus anticoagulant and protein C or S deficiencies. No signs of paroxysmal nocturnal hemoglobinuria on peripheral blood flow cytometry. Patient's bone marrow showed normal trilineage maturation with no signs of any bone marrow disorder.

Discussion and Conclusion

Budd-chiari syndrome is a hepatic venous outflow tract obstruction; it could be primary from veins' thrombosis or phlebitis. Secondary budd-chiari results from a compression or invasion of the vein like in malignancy [1].

Multiple causes of budd-chiari syndrome includes; myeloproliferative disease, hepatocellular carcinoma, thrombosis and hypercoagulable states including; oral contraceptive use, pregnancy, factor 5 leiden mutation, prothrombin gene mutation, antiphospholipids antibody syndrome, protein C or S deficiencies, paroxysmal nocturnal hemoglobinuria and JAK2 mutations. Other immunological conditions are reported and can be idiopathic [2].

Keywords: Myeloproliferative disorders; JAK-2 Mutation; Budd-Chiari Syndrome

Case Presentation

A 41-year-old woman presented with an acute right upper quadrant abdominal pain with increasing abdominal girth for 2 days. She denies shortness of breath, fever, chills, yellowish discoloration of skin and any changes in bowel movements. Her pain was worsening in severity and she presented to the emergency room. She has hypothyroidism. She takes levothyroxine as only medication. She never took an oral contraception pill. She denies history of alcohol abuse or intravenous drug use. No personal or family history of blood clots of any hematological disorders. She has only had one miscarriage.

On physical examination, the patient was not in any distress, temperature 37.2°C, heart rate 72, respirations 18, blood pressure 133/99 mmHg, and an oxygen saturation of 97% on ambient air. The patient had normal heart sounds without any murmurs and lungs were clear to auscultation. Her abdomen was tender and distended no fluid wave and no hepatosplenomegaly. She has multiple recent tattoos on his upper body.

Laboratory work was significant for an elevated Aspartate transaminase (AST) and alanine transaminase (ALT) were 61 U/L and 126 U/L respectively. Prothrombin time (PT), partial thromboplastin time (PTT), total bilirubin, kidney function and electrolytes were within normal limits. Her complete blood

Our patient has a thrombosis to her right hepatic vein as a cause for her BCS. There was no sign of myeloproliferative disease on her bone marrow or peripheral blood counts. The only significant finding was JAK2 mutation positivity.

JAK2 is a tyrosine kinase Janus kinase 2, a gene found on the short arm of chromosome 9 (9p). A mutation in the JAK2 gene leads to constitutive tyrosine phosphorylation activity that promotes hypersensitivity to cytokines and induces erythrocytosis in a mouse model [3]. JAK2 in either exon 14 or 12 was identified in almost all patients with polycythaemia vera, and in about 60 to 65 percent of those with essential thrombocythaemia and primary myelofibrosis [4].

Multiple JAK2 mutations were described, JAK2(V617F) mutation was only associated with BCS. JAK2(V617F) mutations have been positive in 26 to 59 percent of patients with BCS, many of whom had negative results for testing of myeloproliferative disorders (MPD) [5-8]. The incidence of JAK2V617F mutation with BCS and myeloproliferative disorder was about 27% of patients showed upon diagnosis on one of case series [5].

Qi et al. meta-analysis showed that JAK2V617F mutation is frequently found in patients with BCS and portal vein thrombosis, but there is a huge variation of prevalence among the included studies. This mutation was more specific to thrombosis in splanchnic areas [7].

It has been demonstrated that a subset of patients with JAK2V617F MPD have endothelial cells (ECs) that are positive for JAK2V617F and that these cells may possibly contribute to the prothrombotic state [9]. Also this has been demonstrated in some of bone marrow derived of MPD-negative patients and could explain why those patients could develop thrombosis [10].

JAK2V617F mutation could be a pro-coagulant to thrombosis even without myeloproliferative disorders. Although the mechanism is not clear but one of the presumed mechanism; is that JAK-2 is involved in heparanase up-regulation via the erythropoietin receptor which enhances the activity of the blood coagulation initiator tissue factor which leads to increased factor Xa production and subsequent activation of the coagulation system [11].

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