Clinical Case of the Month

A Rare Case of Budd Chiari Syndrome

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INTRODUCTION

Budd Chiari syndrome (BCS) is a rare disorder that results from hepatic venous outflow tract obstruction, occurring anywhere from the small hepatic veins to the suprahepatic inferior vena cava.[1,2] The obstruction can be due to various causes but all result in either reduction or obstruction of hepatic venous outflow. BCS can be further classified as primary BCS, where the obstruction is due to venous disease (such as thrombosis or phlebitis), or secondary BCS in which the compressions or invasion by a lesion originates outside the veins.[1,3] We present a patient with primary BCS.

CASE PRESENTATION

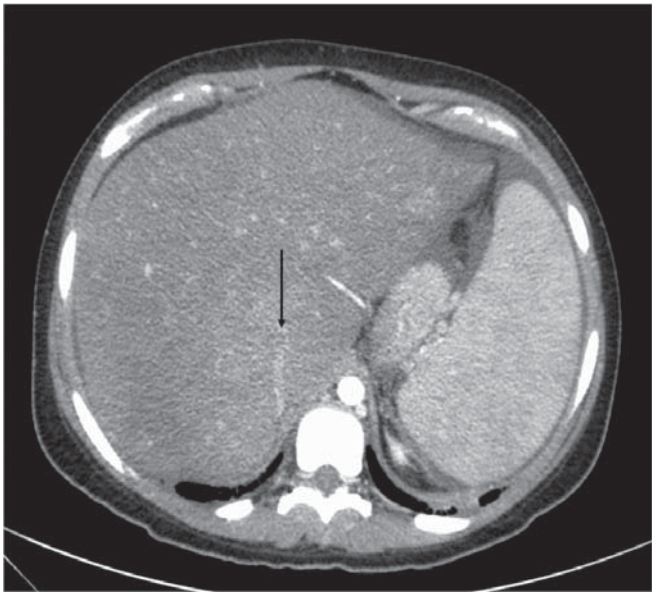

Figure 1. Portal venous phase, axial post contrast image of the abdomen, shows central hepatic hypertrophy causing mass effect on the slit-like IVC (arrow). There is also fatty infiltration of the liver, ascites and splenomegaly.

A 21-year-old woman with a four pack-year history of tobacco smoking and two previous first trimester miscarriages presented to the emergency department with a two-week history of abdominal pain and swelling that followed a flu-like illness six weeks earlier. The patient complained of early satiety followed by right upper quadrant abdominal pain which was dull, non-radiating and 7/10 in intensity. The pain was aggravated by movement and alleviated somewhat by narcotic pain medications. Physical exam at an outside hospital demonstrated the presence of ascites. Two paracenteses and imaging studies failed to reveal a cause for her ascites. The patient was transferred to our facility for further evaluation and management.

On physical exam, the patient had pale conjunctiva without icterus. Abdominal exam revealed a distended abdomen with normoactive bowel sounds, positive fluid wave, shifting dullness, an increased liver span of 20 cm in the right midclavicular line and no guarding, rigidity or rebound tenderness. Extremity exam showed bilateral pedal edema without cyanosis, clubbing, or lymphadenopathy. Genitourinary and pelvic exams were normal.

Laboratory analysis revealed leucopenia with a white blood cell count of 3.3 x 103/UL (4.5-10 103/UL), anemia with a hemoglobin of 11.2 (12.0 -16.0 GM/DL), a hematocrit of 34% (35-46%), MCV of 80 FL (80-100 FL) and RDW of 18% (11.5-14.5%). The patient also had a total bilirubin of 2.1 mg/dL (<1.3 mg/dL), a prothrombin time of 20.8 sec (10.0-13.2 sec), an International Normalized Ratio (INR) of 1.7 (0.9-1.1) and a patial tromboplastin time (PTT) of 38.9 sec (24.0-38.0 sec). Acute viral hepatitis, human immunodeficiency, acute Epstein-Barr Virus titers, cytomegalovirus IgM and IgG, urine pregnancy test, anti-nuclear antibody, SS-A, anti-smooth muscle antibody, anti-mitochondrial antibody and serum and urine protein electrophoresis were negative.

A computed tomography (CT) scan of the abdomen and pelvis revealed hepatomegaly, ascites and the abnormal appearance of intra-hepatic veins and intra-hepatic portion of

inferior vena cava. Hepatic venogram showed an edematous mass effect on the hepatic veins and a clot in the right hepatic vein with spider web collaterals (Figures 1 & 2). Intravenous heparin therapy was begun.

Additional work up revealed a JAK2 mutation and a heterozygous factor V Leiden mutation. Protein C activity was 37% of predicted (74-151%), with an anti-thrombin 3 level of 63 (75-135). The protein S level was 74% of predicted (60-145%), homocysteine level was 5.5 uMOL/L (<10.4uMOL/L); lupus anticoagulant and anticardiolipin studies were negative. The prothrombin gene G20210A mutation was absent and a parosysmal nocturnal hemoglobinuria screen was negative. The patient's liver pathology results showed sinusoidal congestion and hemorrhage, as well as extensive fibrosis and ductular proliferation with no clear cholestasis. (Figure 3) These findings were suggestive of obstruction of hepatic veins/venules as seen in BCS. The patient's abdominal pain and distention improved greatly with anticoagulation and she was discharged on Warfarin with follow-up scheduled with the Hepatology and Hematology specialists.

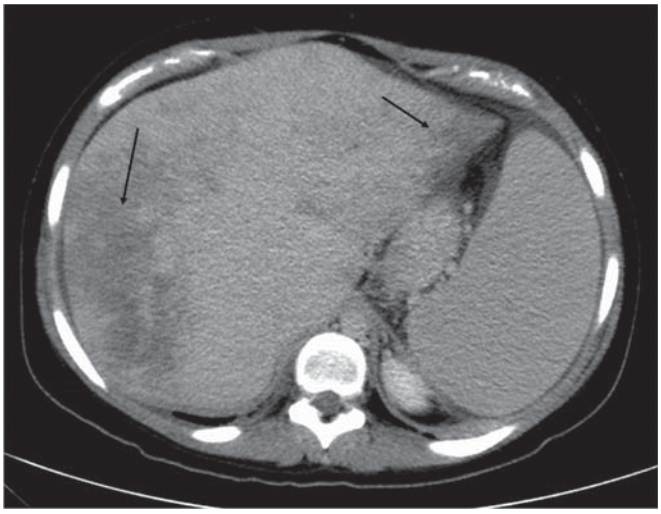

Figure 2. Axial postcontrast imaging of the liver after a five minute delay reveals heterogenously decreased enhancement (arrows) peripherally and homogenous, increased enhancement centrally.

DISCUSSION

BCS is a rare condition with an incidence of 1 in 2.5 million persons per year.[2] Underlying causes of BCS include hypercoagulable states, myeloprolifereative disorders, malignancies, infections and benign lesions of the liver, oral contraceptives, pregnancy and post-partum state.[1-5] Thrombophilic disorders are identified in 84-87% of patients.[1,2]

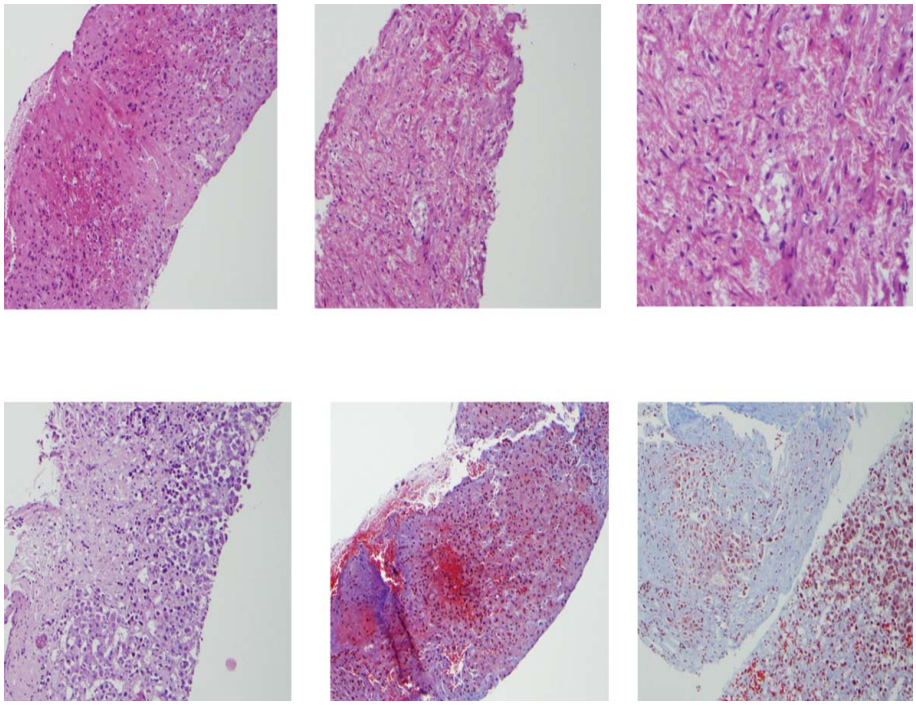

Figure 3. Liver Biopsy: sinusoidal congestion and hemorrhage, extensive fibrosis and ductular proliferation with no clear cholestasis. It is suggestive of obstruction of hepatic veins/venules as seen Budd Chiari Syndrome.

Case series data suggest that BCS occurs in the setting of more than one hypercoagulable state as much as 46% of the time.[2] Despite the strong association with hypercoagulable states, approximately 20% of cases of BCS are identified as idiopathic. The most common causes of thrombophilia in patients with BCS are JAK2 mutation positive myeloproliferative disorders (40%), followed by factor V Leiden (6.8-31.8%) mutation and prothrombin G20210A mutation (0-.64%).[5] JAK2 is the cytoplasmic tyrosine kinase, Janus Kinase 2, a protein associated with hematopoiesis. The gene is located on the short arm of chromosome 9 (9p). A mutation of the JAK2 gene gives rise to constitutive phosphorylation of tyrosine kinase, leading to erythrocytosis and a hypercoagulable state.

The obstruction of hepatic outflow in BCS leads to an increase in sinusoidal pressure, resulting in portal hypertension. The venous stasis also causes increased hepatic congestion and decreased hepatic perfusion leading ultimately to hepatic fibrosis and cirrhosis.[6] The clinical presentation of BCS depends on the acuteness of presentation and degree of obstruction. Patients can present with fulminant, subacute or chronic hepatic failure.[3] Because the acute form of BCS can share commonalities with other causes of fulminant hepatic failure, simultaneous work up of viral, infiltrative, ischemic, malignant and toxin-associated hepatitis is important.[1] Unlike the acute presentation of BCS, where serum aminotransferases, alkaline phosphatase and serum bilirubin can be markedly elevated, the patient with subacute and chronic BCS may present with normal or only mild elevations in serum aminotransferases, alkaline phosphatase and serum bilirubin.[1,2]

BCS occurs most frequently in the third and fourth decade of life and more commonly in women than men. In one study, a very low percentage (< 1.5%) of all acute liver failure was due to BCS.[7] In fact, up to 20% of the patients may not have any symptoms.[1,2,3] The two most commonly associated symptoms of BCS are ascites and abdominal pain.[3] Other classical signs and symptoms include hepatomegaly, fever, splenomegaly, lower extremity edema, gastrointestinal bleeding and hepatic encephalopathy.[1, 2,3]

The diagnosis of BCS can be established noninvasively by using Doppler ultrasonography (US), CT-scan or magnetic resonance imaging (MRI). Doppler US reveals a decrease or absence of hepatic venous flow and parenchymal heterogeneity.[6] Similarly, CT and MRI can also show thrombosis and hepatic venous outflow obstruction. Helpful hints about the duration of BCS from radiological imaging can also be obtained, such as evidence of collateral circulation, signifying that the obstruction is at least subacute or chronic.[6] Evidence of cirrhosis with regenerative nodules implies chronic BCS.[6] The most prominent features noted on noninvasive imaging are hepatomegaly and caudate lobe hypertrophy.[6] Although US, CT and MRI are commonly used to diagnose BCS, the gold standard is hepatic venography.[1] Liver biopsy can help diagnose BCS in acute or subacute cases and it can also help direct treatment options.[6] For example, patients with evidence of cirrhosis may not benefit from revascularization procedures when compared to those without cirrhosis. Serial liver biopsies can also be used to determine response to therapy.[6] A repeat liver biopsy after an intervention that demonstrate improved congestion and hepatocyte recovery can indicate appropriate response to treatment.

The goal of treatment for BSC is to relieve the hepatic congestion that results from the obstruction of venous outflow in order to improve liver perfusion and preserve functioning hepatocytes. There are medical, interventional radiologic and surgical treatments available for BCS. Medical treatments include oral anticoagulation to prevent recurrent thrombosis and extension of an existing thrombosis. Local and systemic thrombolysis can also be used for acute and subacute BCS of less than four weeks duration.[8] Thrombolytic agents are not used to treat the chronic form of BCS, as it can lead to major bleeding complications. Ascites can be treated with a low sodium diet and diuretics. Repeated paracenteses are used for ascites' refractory to low sodium diet and diuretics. In cases of secondary BCS, treating the underlying cause is essential to relieve symptoms. Medical treatment alone has

poor long-term results and only 20% of patients with BCS will respond to medical treatment alone.[6] Radiological and surgical interventions include balloon angioplasty, metallic stents, transjugular intrahepatic portosystemic shunting (TIPS), shunting procedures and liver transplantion.[6,8] Angioplasty and stents are commonly employed in cases of focal stenosis, and TIPS has been used both for therapy, as well as a bridge to transplant.[3,6] Different surgical shunting procedures, including portacaval shunts, splenorenal shunts and mesocaval shunts, have been used to alleviate symptoms in BCS.[9,10] Patients presenting with end-stage liver disease from BCS will benefit from liver transplantation.[10]

Treatment for BCS is individualized. Since most patients with BCS have an underlying hypercoagulable disorder, most will require chronic anticoagulation. For instance, the patient in our case who has JAK2 mutation will require lifelong anti-coagulation. Patients with JAK2 mutation will also require close monitoring with at least yearly follow-up to assess for the development of overt myeloproliferative diseases such as polycythemia vera. There is a high incidence of major bleeding in BCS patients taking oral anticoagulation; however, the fatal bleeding risk is not different from those with venous thromboembolism requiring anticoagulation.[11] Patients with a condition that can be corrected surgically or through radiologic intervention, such as those with inferior vena cava webs, may be the exceptions to this rule. Patients with myeloproliferative disorders may benefit from aspirin and hydroxyurea during the course of the disease.[1] Recent studies show surgical shunting is being replaced by radiological interventions such as TIPS.[2]

With new, less invasive procedures and better treatment options, overall survival is improving.[2] For example, overall survival is commonly reported as high as 90% at six months, 82-87% at one year, 82% at two years and 80% at five years.[1,2] Independent variables predicting worse prognosis include the presence of encephalopathy, ascites, an International Normalized Ratio (INR) of > 2.3, low serum albumin and higher bilirubin concentrations.[1] A retrospective study showed that older age at diagnosis, more severe liver failure and presence of refractory ascites are also associated with worse prognosis. The success rate with liver transplant is variable according to the existing literature; however, the overall survival rate after liver transplant according to the European liver transplant registry is 76% at one year, 71% at five years, and 68% at 10 years.[1] The main causes of death for patients with BCS are liver failure, multiorgan failure and gastrointestinal bleeding.[2] However, in patients with underlying myeloproliferative disease and adequate treatment of BCS, the increased risk of developing neoplastic diseases poses a great risk for their long term survival.[1]

SUMMARY

Budd Chiari syndrome is a rare disorder resulting from hepatic venous outflow tract obstruction anywhere from the small hepatic veins to the suprahepatic inferior vena cava. This patient has a hypercoagulable state secondary to heterozygous mutation of factor V and the JAK2 mutation and is being anticoagulated. We hypothesize that the low protein C and low antithrombin III levels seen in this patient resulted from decreased synthetic function of the liver and were not indicative of actual deficiencies. Indeed, reports of coexisting protein C and antithrombin III deficiencies are not existent in the literature and likely are not compatible with life. All patients with BCS warrant a hypercoagulable work up and JAK2 mutation is increasingly recognized as a contributing factor, even in those patients without obvious signs of polycythemia vera.

REFERENCES

1. DeLeve LD, Valla D-C, Garcia-Tsao G. Vascular Disorders of the Liver. *Hepatology*. 2009;49:1729-1761.
2. Murad SD, Plessier A, Hernandez-Guerra M, et al. Etiolgoy, Management, and Outcome of the Budd Chiari Syndrome. *Annals of Internal Medicine*. 2009;151:168-175.
3. Valla D-C. Primary Budd Chiari Syndrome. *Journal of Hepatology*. 2009;50:195-203.
4. Sozer S, Fiel MI, Schiano T, et al. The presence of JAK2V61F mutation in the liver endothelial cells of patients with Budd Chiari Syndrome. *Blood*. 2009;113:5246-5249.
5. Shetty, S, Ghosh K. Thrombophilic dimension of Budd Chiari syndrome and portal venous thrombosis – A concise review. *Thoramb Res*. 2010. Article in press.
6. Cura M, Haskal Z, Lopera J. Diagnostic and Interventional Radiology for Budd Chiari Syndrome. *RG*. 2009;29:669-681.
7. Ravi M, Shanmugam V, Gunson B, et al. Aetiolgy and outcome of acute liver failure. *HPB*. 2009;11:429-434.
8. He X-H, Li W-T, Peng W-J, et al. Anticoagulation with Warfarin for Budd Chiari Syndrome with Chronic Inferior Vena Cava Thrombosis: An Initial clinical Experience. *Ann Vasc Surg*. 2010. Article in Press.
9. Cameron JL, Herlong HF , Sanfey H, et al. The Budd-Chiari Syndrome. Treatment by Mesensteric-Systemic Venous Shunts. *Ann. Surg*. 1983;98:335-344.
10. Haff G, Todo S, Tzakis A, et al. Transplantation for the Budd-Chari Syndrome. *Ann. Surg*. 1990;211:43- 49.
11. Rautou P-E, Douarin L, Denningers M-H, et al. Bleeding in patients with Budd-Chiari Syndrome. *Journal of Hepatology*. 2011;54:56-63.

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