Budd Chiari Syndrome- An Overview

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Abstract: Budd-Chiari syndrome (BCS) is a serious, rare but life-threatening condition of the liver and requires immediate and aggressive medical interventions. Patients with BCS often have predisposing multiple prothrombotic factors for development of the disease. The epidemiology of BCS in the West and Asian countries differs greatly due to the various epidemiological characteristics in each of these regions. Recent studies suggest that a step wise strategical treatment approach have proven to have an excellent 5-year survival rate. Transjugal intrahepatic portosystemic shunting and percutaneous transhepatic balloon angioplasty are the effective options in patients with hepatic obstruction. Orthotopic liver transplantation will be invariably required for those patients who are unresponsive to revascularization and TIPS. Other medical interventions are aimed at controlling further development of ascites and reducing the extent of thrombi in the hepatic veins and IVC. This review seeks to summarize the salient aspects of this medical condition and the various presentations seen with it.

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I. Introduction

CASE PRESENTATION

We report a case of a 24-year-old female who presented with chief complaints of abdominal pain and discomfort for 1 week. She also had a history of fever of 1-week duration and abdominal distension for 2 weeks. Abdominal ultrasound revealed moderate ascites, bilateral minimal pleural effusion and thickened and edematous gall bladder secondary to ascites. A Doppler ultrasound of the liver showed left hepatic vein thrombosis. Abdominal CT revealed hepatomegaly with hepatic vein thrombosis and mottled liver enhancement, gall bladder edema, bilateral perinephric fluid and bilateral pleural effusion. A fluid cytology was performed at this point which showed occasional lymphocytes, reactive mesothelial cells in an eosinophilic proteinaceous fluid background.

A complete blood count revealed microcytic hypochromic anemia (Hb-9.4mg/dl) and neutrophilic leukocytosis. Liver function test revealed hypoalbuminemia, with decreased albumin levels: 30g/L lab (Normal range:35-50g/dl), increased bilirubin levels TBL: 2.0mg/dl (Normal:0.3-1.2mg/dl), IBIL: 1.1mg/dl (Normal:0.2-0.6mg/dl) and normal levels of Transaminases, Alkaline phosphatase :106U/L (Normal:0-240U/L), Gamma Glutaryl Transeptidase: 64U/l (Normal :6-24U/L), Albumin/ Globulin ratio (A/G): 0.9g/dl. Prothrombin time and International Normalized Ratio (INR) were elevated, Prothrombin time: 22.0 seconds and INR of 1.79. Immunoassasy revealed AFP: 2.50 IU/ml and Beta HCG: 0.5 IU/ml. Hepatic antibodies and HbsAg were both non-reactive. Fasting lipid profile, kidney and thyroid profile were normal. A diagnosis of Budd Chiari syndrome was made as the patient had the triad of abdominal pain, ascites and hepatic vein thromboses.

The patient was therefore managed conservatively with anticoagulants, proton pump inhibitors, anti-emetics, diuretics & antibiotics. USG Guided ascitic tapping was done during the course of treatment and hospital stay and about 3 liters of fluid was tapped by paracentesis. Patient improved symptomatically and hence was discharged with hepato-protective agents such as ursodeoxycholic acid and vitamin supplements (lecithin, silymarin, glutathione, zinc, amino acids & vitamins.)

II. Definition

Budd-Chiari syndrome is an uncommon disorder of the liver which is characterized by the obstruction of hepatic venous outflow (congestive hepatopathy) at any level between the small hepatic veins and the right atrium. The disease is life threatening and fatal if not treated properly. (1, 2) Portal hypertension is an invariable outcome in this situation. (3) BCS was initially described as a symptomatic obstruction of the hepatic veins and then it was subsequently broadened to a term as hepatic venous outflow tract obstruction which included the obstructive lesions of the suprahepatic portion of inferior vena cava (IVC). (4) Patients with BCS often have a combination of multiple prothrombotic factors which include myeloproliferative neo-plasms and antithrombin deficiency. (5-7) The most common morphologic feature of BCS is thrombosis, unrelated to any other structural abnormality, and the most common location is the large hepatic vein. (5) The occurrence of the
splanchnic vein thrombosis is not defined properly and there is variation on the estimates depending on the data sources available.(8) BCS is considered to be a disease of the liver presenting with a classic triad of hepatomegaly, ascites and abdominal pain resulting in subsequent hepatic dysfunction.(9-11)

III. History

George Budd, a British internist, described three cases of hepatic vein thrombosis due to abscess-induced phlebitis in the year 1845, and Hans Chiari, an Austrian pathologist, documented the first pathologic description (histopathology) of a liver with endophlebitis of the hepatic veins in the year 1899. Thus, the disease came to be termed as Budd Chiari syndrome. (1,7)

IV. Epidemiology

Patients of BCS with IVC membranous obstruction are widely distributed across the globe. Certain regions such as South Africa, Nepal, India and China particularly along the Yangtze (yellow river) have a higher prevalence suggesting that the cause of BCS may be due to certain epidemiological factors such as environmental factors, living habitat, and microbial infections around these areas.(4,7) BCS has a prevalence of a one in a million of the general population. In the West, the incidence of BCS per year is 1 in 2.5 million. In Western countries, Factor V Leiden and factor II Gene mutations are seen in about 25% and 5% of the patients with BCS respectively.(1) Geographical differences in these underlying risk factors could explain the variation in anatomical site of disease progression with poverty being more common in Asia and oral contraceptive use and myeloproliferative disorders being a cause.(6) Various studies have shown us the incidence of BCS in different countries. A population based nation-wide study in Asian country involving a total of 424 patients with BCS in the year 2016 revealed that the prevalence of BCS is higher in Asian countries.(12,13) Membranous obstruction is the commonest cause of BCS in the Chinese population. (14) BCS is known to affect all age groups but is more common in people between 30-40 years.(15)

V. Clinical manifestation

BCS can have a diverse range of presentations ranging from acute liver failure to being totally asymptomatic and incidentally detected doing a radiological investigation. Abdominal pain, with ascites, portal hypertension, splenomegaly and hepatomegaly are common features on history and examination. These symptoms are commonly present in patients with BCS that is arising due to the occluded hepatic veins and IVCs.(6,15,16) 15-20% of BCS patients are asymptomatic due to the fact the only one of the hepatic vein has thrombus obstruction and the rest of the venous blood flow is carried out by the other large vein collaterals.(6,17) Other clinical features include fever, pedal edema and truncal hepatic veins. Less common clinical manifestations include esophageal varices and hepatic encephalopathy which may be due to the fulminant hepatic failure. The presentation of BCS depends on the extent and rapidity of hepatic venous outflow obstruction and the presence of decompressing venous collaterals. (6) Sinusoidal obstruction with ischemia of the hepatic cells may be a reason for fulminant liver failure can be seen in patients with BCS. (15,16)

VI. Classification

BCS can be classified according to etiology, site of obstruction, manifestations and duration of the disease.(3,4) BCS is regarded as primary if the flow is obstructed because of the primary venous entity, usually a thrombosis, with primary hematological disorders and hypercoagulable conditions.(3,7) Primary BCS is of multifactorial origin where several prothrombotic factors altogether predisposes the individual to develop thrombi in the hepatic veins.(10, 17, 18) BCS is regarded as secondary when the hepatic blood flow is obstructed by compression or the invasion of a lesion outside the hepatic venous outflow track (benign or malignant tumors, abscess, cysts and so on) or IVC with a thrombus.(3,7) According to the location of the block, it is classified as small hepatic veins, large hepatic veins, interior vena cava or a combined level of obstruction.(3,19-21)

According to the location of the obstructed vein it’s is defined as truncal (type 1) - thrombosis or HV obstruction without IVC compression or any obstruction, radicular type (type 2) - thrombosis or HV obstruction with the IVC compression or any obstruction, occlusion of the major hepatic veins, venoocclusive type (type 3) - isolated hepatic venous webs ( spider web pattern of collateral veins ) which causes the occlusion of the small centriflobular veins and (type 4) - isolated IVC webs.(7,22)

According to the duration of disease, BCS is classified as fulminant type with hepatic encephalopathy within 8 weeks of development of jaundice, acute which lasts for a short duration of less than a month, subacute in which there is an insidious onset usually lasting for about 1-6 months & chronic which lasts for a longer duration usually greater than 6 months. The chronic type has complications of cirrhosis.(22)
VII. Causes Of Budd-Chiari Syndrome

Thrombosis or obstructed hepatic veins are the primary cause of BCS. Primary endophlebitis and congenital malformations are rare cause of BCS.(23) The most commonest causes include acquired and inherited hypercoagulable states.(17, 24)

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Hormonal Factors (women only)</th>
<th>Myeloproliferative Disorder or JAK2 Mutation</th>
<th>Systemic (Various disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Any acquired disorder</td>
<td>1. Oral contraceptive use in women due to high estrogen content.</td>
<td>1. Any Myeloproliferative disorder</td>
<td>1. Aspergillosis</td>
</tr>
<tr>
<td>5. Inherited Thrombophilia</td>
<td></td>
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<td>5. Hepatocellular carcinoma</td>
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<td>6. JAK2 V617F mutation in patients</td>
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<td>6. Inflammatory bowel disease (IBD)</td>
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<td>7. Deficiency of vitamin-C &amp; protein-S</td>
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<td>7. Membranous obstruction of inferior vena cava (IVC)</td>
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<tr>
<td>8. Hereditary thrombotic disposition</td>
<td></td>
<td></td>
<td>8. Trauma</td>
</tr>
</tbody>
</table>

VIII. Diagnostic Work-Up

The main aim in the diagnosis of BCS is to assess the liver injury and the etiologic factors of the disease. (3) Diagnosing BCS can be usually difficult due to the varying spectrum of symptoms due to the extent of severity of liver damage.(11)

BCS should be ruled out in patients with

- A sudden and abrupt onset of ascites with painful hepatomegaly.
- A massive ascites with decreased liver function.
- Fulminant liver failure which is either related to ascites and hepatomegaly.
- A sudden unexplained chronic liver disease without a specific cause.
- Hepatic disease with an obstruction due to a thrombogenic disorder.(1)

In patients presenting with BCS, the initial step in diagnosis is to evaluate and consider the signs and symptoms of hepatic venous flow obstruction such as painful hepatomegaly or ascites which may be acute or refractory.(6) In BCS patients, the ascitic fluid will be similar to that of ascites in cardiac patients consisting of SAAG (greater than 1.1g/dl) & high protein count (greater than 2.5 g/dl).(6,28)

A panel of laboratory tests comprising of hematological investigations, kidney and liver function tests, INR or PT are effective in the diagnosis of BCS.(6) One-time diagnostic work up for BCS include retrograde Co2 photography, hepatic venography and inferior vena cava pressure monitoring done during the treatment simultaneously.(11)

Documentation of various parameters in BCS can be done by hemogram, genetic factor identification test for factor V & prothrombin, detecting the coagulation factors & its inhibitors, antiphospholipid antibody and lupus anticoagulant testing.(1)

The hepatic obstruction can be determined by various techniques such as the Doppler ultrasound, computed tomography (CT), MRI (Magnetic resonance imaging) which are the non-invasive methods. As Doppler ultrasound is highly specific and sensitive method, it is considered as the first choice in the diagnosis of BCS. The various features of BCS in the Doppler are large hepatic vein with a turbulent reversed or an absent blood flow, A large intrathoracic or subcapsule collaterals of vein with a continuous blood flow, spider web like appearance at the area of the hepatic vein obstruction with the absence of blood flow in that area /absence of hepatic vein wave form without flutter/ an hyperechoic cord replacing the normal hepatic vein. Other non-invasive techniques are not as effective as the Doppler. Magnetic resonance imaging (MRI) and Computed tomography (CT) are also used to visualize the hepatic vein specifically, the hepatic parenchyma which helps to
detect precisely the obstructed areas of necrosis or reduced perfusion.(6) Ultrasound Doppler is the follow-up imaging test of choice for follow-up testing in patients with BCS.(22) Splenoprontography can be done to evaluate the varices in the lower esophageal region and also the gastric fundus in patients with BCS.(15) Liver biopsy is not an ideal method for diagnosing BCS because there is a high risk of sampling errors.(29,30) In catheter venography, precise anatomic & histologic information can be identified by performing a transjugular biopsy of liver.(31)

**IX. Treatment Strategies**

Treatment for BCS is a must as it is a life-threatening condition with a high mortality rate. Over the past years, the treatment has been fairly standardized for BCS. (2) Primary goal of treatment in BCS is to eliminate mortality and reduce the morbidity. Medical interventions aims at controlling further progression of ascites, reducing the extent of thrombi in the hepatic veins & IVC, and determining the underlying cause.(20,23) Strategy in the management of abdominal ascites includes reducing the patient daily intake of sodium which should be 60-90 mEq/dl that is equal to about 1500-2000 mg of salt.(32, 33) For all patients with BCS, consider lifelong anticoagulant therapy regardless of the etiological factor, treat the underlying pro-coagulant condition as necessary, and carry out hepatocellular carcinoma surveillance monitoring.(2,5,23) Vitamin-K antagonists are substituted instead of heparin within 2-3 weeks after initial treatment, targeting an INR (international normalized ratio) of 2-3.(34) 1 and 2 year survival rates are good with contemporary management, which includes the other noninvasive therapies (anticoagulants and diuretic agent) and invasive techniques.(2) The therapeutic interventions for BCS is same in children and adolescent age group.(35) In patients with portal hypertension (patients who are symptomatic) consider hepatic vein interventions and if feasible perform dilatation and stenting.(2)

**TIPS & PTBA**

Transjugular intrahepatic portosystemic shunting (TIPS) is a procedure of choice for patients who have acute variceal bleeding that is non-responsive to endoscopic treatment and also in patients who have rebleeding within 5 days. Early TIPS procedure is especially recommended in patients with increased predisposition to treatment failure. However, pharmacological and endoscopic therapy are to be carried out initially within the first 24 hours. In patients who have already had bleeding events, there is a high risk of rebleeding coupled with mortality risk. In this context endoscopic ligature coupled with pharmacological therapy such as propanalol, nadolol can be initiated. Failure of the above therapy warrants treatment with TIPS placement using a stent graft. However hepatic encephalopathy is one of the dreaded complications that can occur in patients receiving TIPS therapy. Non-response to beta blockers in patients with ascites is another situation where TIPS procedure may be attempted. Studies have also shown that the survival outcomes are better with TIPS procedure compared to paracentesis risk prediction. The Garcia-pagan score is a risk prediction tool to identify patients who have a high predilection for death or requirement of liver transplantation following TIPS procedure.(37) Some of the situations where TIPS implantation should be avoided include right heart failure, liver cysts in the puncture path, uncontrolled systemic inflammation or sepsis, untreated bile duct obstruction, severe pulmonary hypertension (greater than 45mmhg) & child-pugh score greater 13 points.(38)

Besides TIPS, the other interventional procedure for the management of HV lesions in BCS includes percutaneous transhepatic balloon angioplasty (PTBA) and endovascular stent implantation. Stenting has been recommended as the first line decompressive procedure in those patients with IVC or HV stenosis. Failure with these procedures would require the patients to be offered TIPS. Angioplasty is also a suitable procedure for patients with obstruction due to membranous webs.(34)

**LIVER TRANSPLANTATION**

In patients with decompensated liver cirrhosis, liver transplantation may be the only viable solution. Those patients who have failed portal decompressive procedures may also be salvaged with liver transplantation. The long-term clinical outcomes following liver transplantation are found to be acceptable in most studies. However, these patients need life-long anticoagulation.(34)

**X. Conclusion**

Budd-Chiari syndrome is life threatening and requires immediate medical attention. The diagnosis and management of BCS in acute and chronic stages of liver disease must be established promptly. Recent studies have shown that a stepwise treatment strategy is effective in patients with BCS. Other invasive techniques like TIPS and PTA have been proven to be effective. Further research is needed to determine the precise role of MRI for differentiating benign liver nodules with HCC in BCS patients.(6) Prognostic score can be calculated from model for end-stage liver disease (MELD), Rotterdam index, original Clichy score & Child-Turcotte-Pugh (CTP), in predicting the mortality rate, clinical outcome, and if there any need for re-interventions.

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Reference


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