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BUDD CHIARI SYNDROME: VARIOUS CASE PRESENTATION

General Medicine

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KEYWORDS

INTRODUCTION

Budd-Chiari syndrome (BCS) is a heterogeneous group of complete or partial hepatic venous tract outflow obstruction conditions, regardless of the type of mechanism. The hepatic venous outflow obstruction leads to increased hepatic sinusoidal pressure which results in liver congestion and portal hypertension,which leads to hepatocyte hypoxia and dysfunction. If the condition remains under-recognized and the obstruction is not corrected in a timely manner, this can lead to hepatocyte necrosis, progressive centrilobular fibrosis, nodular regenerative hyperplasia, and ultimately cirrhosis [1-4].One or more underlying prothrombotic conditions are observed in at least 75% of patients with primary BCS[5,6]. The systemic prothrombotic conditions are divided into acquired and inherited types. Acquired causes primarily include myeloproliferative neoplasms (MPNs), hyperhomocysteinemia, Paroxysmal Nocturnal Hemoglobinuria (PNH) and Behçet's syndrome, etc. Inherited causes primarily include factor V Leiden mutation, G20210A prothrombin gene mutation and inherited protein C, protein S, and antithrombin deficiencies.Most common acquired causes of primary BCS are BCR-ABL negative MPNs, including polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis[7,8].

The prevalence of MPNs is about 50% in BCS patients [14]. Because JAK2 V617F mutation is found in about 80% of patients with polycythemia vera and 50% of patients with essential thrombocythemia or idiopathic myelofibrosis, routine screening for JAKV617F mutation is very valuable to establish an early diagnosis of MPNs in BCS patients. Numerous observational studies and meta-analyses confirm that the JAK2V617F mutation can be detected in 30-50% of BCS patients[10-14]. By comparison, hyper-homocysteinemia, PNH, and Behçet's syndrome appear to be relatively rare etiologies of BCS. However, several important points should be clearly recognized. First, a systematic review and meta-analysis suggests that hyper-homocysteinemia with homozygous MTHFR mutation may be associated with the occurrence of BCS[15].Second,PNH is an extremely rare condition[21-23] . However, the presence of hepatic vein thrombosis is extraordinarily high in patients with PNH[24] .

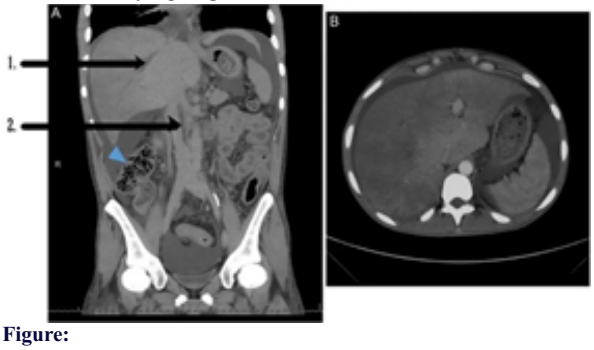

Figure:
CT abdomen Coronal view suggestive of:
1.Thrombosis in common hepatic vein
2. partially occluded IVC

Table 1. Three Types Of BCS According To Level Of Obstruction [40]

Type	Level of obstruction
1	Obstruction of IVC with or without secondary hepatic vein occlusion
2	Obstruction of major hepatic veins
3	Obstruction of the small centrilobular venules
BCS, Budd-Chiari syndrome; IVC, inferior vena cava	

Inherited protein C, protein S, and antithrombin III deficiencies are also considered as the major risk factors for BCS. However, their roles are ambiguous, because chronic liver diseases often obscure the recognition of these deficiencies. Recently, a systematic review and meta-analysis confirms that inherited protein C, protein S, or antithrombin deficiencies should significantly increase the risk of BCS [25]. Accordingly, the measurement of protein C, protein S, or antithrombin concentrations should be regularly performed in BCS patients and their first-degree relatives.

Table 2. Classification Of BCS According To The Duration Of Disease [41,42]

Type	Duration
Fulminant	Present with hepatic encephalopathy within 8 days of development of jaundice
Acute	Short duration (<1 month), ascites, hepatic necrosis without formation of venous collaterals
Subacute	Insidious onset (1–6 months), ascites, minimal hepatic necrosis, and portal and hepatic venous collaterals
Chronic	(>6 months) Complications of cirrhosis in addition to findings in the subacute form

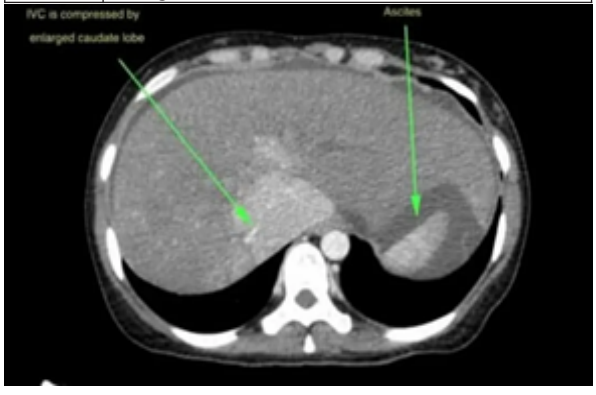

Figure: Transeverse view of CT liver suggestive of diffuse hepatic injury *sparing Caudate lobe*

Here, we discuss three cases of Budd Chiari Syndrome with different etiologies presented to Civil Hospital Ahmedabad.

Case:1 BCS With Myeloproliferative Disorder

A 54 year old female presented with chief complain of right hypochondriac pain for 1 month. On examination, Patient's vitals were

normal. There were no signs of icterus, clubbing, cyanosis, pallor, lymphadenopathy or edema. On systemic examination, hepatosplenomegaly was present with rest all normal. On ultrasonography Liver:15.5 cm with altered and coarse in echotexture and absence of doppler perceptible flow in hepatic veins that is suggestive of Budd chiari syndrome. On blood investigation, Hb:13.6 gm/dl; Total leucocyte counts: 14300/cmm; Platlets: 6.40 lac/cmm suggestive of thrombocytosis. On liver function test, Total Billirubin:0.48 mg/dl, direct bilirubin:0.22 mg/dl, SGPT:17 IU/L, SGOT: 25 IU/L, S.ALP: 93 U/L were noted. Coagulation profile showed PT:15.7 seconds with INR of 1.35 , aPTT: 48 seconds. Based on thrombocytosis bone marrow biopsy was planned which showed magakaryocytic proliferation along with increased number of mature megakaryocytes with rest cell lineages were normal. On further investigation patient was found to be positive for JAK 2 PCR mutation. Thus, diagnosis of myeloproliferative disorder was made. Patient was treated with short course of subcutaneous low molecular weight heparin bridged with warfarin. Patient was explained regarding bleeding tendencies and advised for regular monitoring of coagulation profile. Patient was also started on tablet hydroxyurea 15mg/kg/day for thrombocytosis and explained regarding possible side effects of it.

Case:2 BCS In Case Of Protein C & S Deficiency

A 16 year old female from peripheral center was referred to our hospital with chief complain of abdominal distension for 15 days. On examination, Patient was vitally stable.On systemic examination, abdomen was tense and non tender, with positive fluid thrill, rest systemic examination was normal. On Patient's blood investigations, Hb:8.7 gm/dl; Total Leucocyte Count:10340/cumm; Platelet count:2.82 lac/cumm. Liver function test showed total bilirubin:1.08 mg/dl, direct bilirubin:0.64 mg/dl; SGPT:231 IU/L; SGOT:234 IU/L. Total serum protein: 5.10 gm/dl, S.Albumin: 2.60 gm/dl; Globulin:2.50 gm/dl. On ascitic fluid studies, Total protein: 2.61 gm/dl; Sugar: 118 mg/dl. which is transudative in nature.All hepatic viral markers and HIV serology were negative & ANA by IF: Negative. On CECT abdomen, Heterogeneous enhancement of liver and mild caudate lobe hypertrophy was seen with non opacification of the hepatic veins on all phases likely representing thrombosis. There is also significant narrowing/compression of intrahepatic IVC with re-canalization of the umbilical vein and linorenal collateral are seen, findings consistent with budd-chiari syndrome. On further investigation Protein C: 7.794 % (Ref value:70-140%); Protein S:68.1% (Ref value in female:112.5-257.6%). The patient was treated with Human albumin and short course of subcutaneous low molecular weight heparin bridged with warfarin. Patient was explained regarding bleeding tendencies and advised for regular monitoring of coagulation profile.Patient was also advised regarding nature of the disease and possible complications like thromboembolism and related symptoms.

Case:3 BCS In Case Of Protein C Deficiency

A 16 year old female presented with chief complain of yellowish discoloration of sclera, body and urine for 8 days along with nausea for 2 -3 days. On examination, Patient's vitals were normal. On systemic examination, hepatosplenomegaly with liver surface irregularity with rest systemic examination was normal. Abdominal ultrasonography was suggestive of enlarged liver size (16 cm) with altered echotexture and minimal surface irregularity, suggestive of early changes of Liver Parenchymal Disease. Additionally, doppler perceptible flow was absent in right and middle hepatic veins, however, left hepatic vein was having normal flow. Spleen was enlarged in size with 21 cm and normal in echotexture. On blood investigation, Hb: 8.3 gm/dl, Total leucocyte count: 2160/cc, Platlet count :39000/cc; on liver function test, Billirubin (total): 28.2 mg/dl, direct bilirubin : 16.51 mg/dl with SGPT: 31 IU/L, SGOT: 54 IU/L, S.ALP: 79 IU/L. S.Protein(Total): 5.82 gm/dl albumin: 2.82gm/dl, S. globulin: 2.94 gm/dl. Coagulation profile showed Prothrombin time: 18.6 seconds with INR of 1.53, aPTT: 40.2 seconds. Hepatic viral markers were negative. On further investigations patient's investigations are Homocysteine: 10.51 umol/L; Protein C:17.2(Ref value:70-140%)**;** Protein S:113.4 (Ref value in female:112.5-257.6%)**;** Anti Thrombin III : 91.9 (83-128 %). The patient was treated with Antibiotics ,Vitamin K,Beta blocker(Propranalol).Patient was explained for need of liver transplantation.

DISCUSSION

The most common causes for Budd-Chiari syndrome include inherited and acquired coagulable states. The inherited causes include factor V Leiden mutation, protein C and S deficiency, anti thrombin III deficiency and prothrombin G20210A mutation which result in hepatic vein thrombosis and further precipitating to Budd-Chiari syndrome. The acquired causes include myeloproliferative disorders like polycythemia vera, paroxysmal nocturnal hemoglobinuria, essential thrombocytosis and myelofibrosis [27,28,37]. Other conditions which have been reported as risk factors for the development of Budd-Chiari syndrome include anti-phospholipid syndrome, hypereosinophilic syndrome, behcet disease and ulcerative colitis [27]. The pathophysiology of Budd Chiari syndrome includes occlusion of hepatic veins leading to venous outflow compromise in the liver which ultimately results in increase in sinusoidal and portal pressure leading to hepatic congestion and ascites. Hepatocytes undergo ischemic damage that eventually leads to non inflammatory centrilobular cell necrosis. The patient with Budd Chiari syndrome can present as fulminant, acute, subacute and chronic state.[30]

In adults, BCS is often associated with an activation of the hemostatic system due to thrombophilic anomalies or clonal disorders of hematopoiesis as myelo-proliferative disorders [43-49]. In patients with BCS, hemodilution, occult bleeding, and hypersplenism due to portal hypertension may mask the changes in blood cell count. Also, myeloproliferative disorders associated with BCS can present with an atypical phenotype, making the conventional diagnostic criteria elusive [50,55,56]. Some molecular aberration of the ***JAK2*** gene has been proposed as a noninvasive marker for myeloproliferative disorders [51–54]. The Val617Phe ***JAK2*** mutation is a somatic and heterozygous mutation that has been recently reported to occur in some patients with myeloproliferative disorders. Several reports suggest that these patients have an increased rate of thrombosis and often need cytoreductive therapy. This fact, along with the presence of other cases of myeloproliferative syndrome in the family, suggests a familial genetic predisposition to thrombosis.

The acute variant develops within 1 month and is characterized by ascites, abdominal pain, hepatomegaly, elevation of liver enzymes, renal failure and coagulopathy [31]. The subacute form is the most common type and usually insidious in onset and asymptomatic with no ascites [29]. The chronic type of Budd Chiari syndrome is characterized by development of portal hypertension with ascites. The hepatic enzymes can be normal or minimally elevated[29]. Fulminant type develops within a week and patient presents with severe hepatic failure with elevation of enzymes, hyper -bilurubinemia, encephalopathy and coagulopathy[38]. The liver is massively enlarged and painful with ascites[29,31,39].

The general clinical manifestions encountered in Budd Chiari syndrome include abdominal pain, abdominal distension, ascites, lower limb edema, gastrointestinal bleeding and encephalopathy [27,30]. Clinicallly Budd Chiari syndrome should be suspected in patients who present with any of the following : fulminant liver failure with acute onset ascites and hepatomegaly, massive ascites with preserved liver function, unexplained chronic liver disease and an associated thrombogenic disorder[26].

Imaging studies like conventional ultrasound, Doppler ultrasound, CT, MRI and catheter venography are helpful in the diagnosis. The diagnosis of protein C deficiency may be suspected in a patient with recurrent venous thrombosis, thrombosis in an unusual vascular bed (eg; Portal, hepatic, mesenteric, cerebral), thrombosis at a young age (eg, <50 years),Strong family history of VTE, and/or warfarin-induced skin necrosis. The diagnosis is established by laboratory testing that reveals protein C activity below the lower limit of normal in the laboratory performing the testing. Typical values in heterozygotes are approximately 50 percent of normal. In a 2013 meta-analysis of studies involving patients with portal vein thrombosis (PVT) or hepatic vein thrombosis (Budd-Chiari syndrome [BCS]), inherited protein S deficiency was found in 3 percent of each group [57].

In our three cases the patients were diagnosed on the basis of radiological imaging. All of our three patients found to be in subacute budd chiari syndrome. We did extensive workup for thrombophilia and myeloproliferative disorders to find etiologies like protein c & s deficiency and essential thrombocytosis. Acute thrombosis can transiently reduce levels of protein C and S so utility of testing for these disorders in acute phase of thrombosis is limited.

Medical management of Budd Chiari syndrome involves treating the underlying cause and symptomatic treatment accordingly [26,32,39].In

cases of BCS and myeloproliferative syndrome, cytoreductive therapy is often necessary in addition to anticoagulant therapy. In our case, hydroxyurea treatment was adapted to ensure a normal platelet count. Surgical management involves membrane resection, IVC reconstruction, portosystemic shunts, portoarterial shunts and liver transplantation[33-37]. Endovascular management includes balloon angioplasty, stunt placement, catheter directed thrombolysis and Trans jugular intrahepatic portosystemic shunt.

The spontaneous mortality of BCS in adults approaches 70% at 1 year and 90% at 3 years [43,44]. In children, mortality that is either spontaneous or caused by liver failure after shunt surgery may involve 25% of cases [47].

CONCLUSION

BCS can be caused by varying etiologies. While investigating the etiology, we should evaluate the patient for all the prothrombotic states including both inherited as well as acquired and for malignancies. Treatment of BCS should be done according to the symptoms and simultaneously appropriate therapy to target the cause of BCS should be started without any delay.

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