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IDIOPATHIC BUDD CHIARI SYNDROME

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I. Case Presentation:

A 61-year-old female came to the emergency department with a two-week history of bilateral lower limb edema and dyspnoea on exertion. The pedal edema and dyspnoea worsened progressively and now she feels difficulty in doing activities of daily living. But she reports no orthopnoea, chest pain, palpitation, dizziness or diaphoresis. She also felt occasional mild right-sided upper abdominal pain. There was no fever, cough, vomiting, or decreased urine output. There was no history of recent travel outside the state and no history of intake of any drugs or herbal medications.

On general physical examination, she weighed 63 kg. There was no significant distress. Her heart rate was 103/ min, respiration was 22/min, BP was 120/80 mm in the right upper limb in the sitting position and her oxygen saturation was 93% in room air. She had mild icterus and lower limb edema extending up to mid-thigh. However, there was no clubbing, cyanosis, or significant lymphadenopathy. The abdomen was moderately distended and the liver was enlarged 3 cm below the right costal margin. There was no splenomegaly or any palpable mass. Cardiovascular examination revealed normal heart sounds without any murmur but there was mildly elevated JVP. Chest revealed minimal basal crepitations.

All these symptoms led to the suspicion of cardiac failure as the primary cause of these symptoms. The other possible differential diagnoses are renal failure or hepatic failure.

The patient had no symptoms of cough or fever and the chest X-ray was normal except a mildly elevated right hemidiaphragm which ruled out the possibility of pneumonia, pneumothorax, and pleural effusion.

Even though the patient had symptoms of fluid overload, she had no history of reduced urine output, and the initial creatinine was 1.14 which ruled out renal failure as a cause of the current symptoms.

The findings of tachycardia, low oxygen saturation, and elevated d-dimer mandated CT pulmonary angiogram which ruled out pulmonary embolism. A bilateral lower limb venous doppler was done which ruled out lower limb venous thrombosis. Echocardiogram was also done and found to be normal ruling out the cardiac causes of these symptoms.

The upper abdomen cuts visualized during the CT chest showed an edematous liver and moderate ascites. So ultrasound of the abdomen was done which confirmed the same findings and also showed the presence of gallstones and reduced flow through the portal vein. Elevated total bilirubin, mildly reduced albumin (3.4 g/dl), transaminitis, and ascites prompted for further evaluation. Paracentesis was done and ascitic fluid analysis showed high SAAG (>1.1) ascites suggestive of portal hypertension. The patient was started on furosemide and intravenous albumin.

In suspicion of portal vein thrombosis, a medical gastroenterologist was consulted and an MRI of the abdomen was done which showed patent portal veins but there is limited flow through hepatic veins, altered liver parenchyma with moderate ascites, and marked caudate lobe enlargement. These findings pointed to the possibility of veno occlusive disease and hence, Doppler ultrasound of hepatic veins was suggested.

In the meantime, her urine output decreased progressively and her RFT worsened on day 3 of the hospital stay. She had mild confusion and asterixis. The LFTs and INR worsened and her ammonia was elevated. She was diagnosed with fulminant hepatic failure and hepatic encephalopathy and started on anti-encephalopathy measures. Due to worsening renal functions and oliguria, nephrology was consulted and she was started on hemodialysis on day 5.

Investigations were done to evaluate for causes of fulminant hepatic failure. Viral panels including hepatitis viruses A, B, C, D, E, and EBV are negative. Serum ceruloplasmin and autoimmune hepatitis workup are also negative. Serum iron studies and alpha 1 antitrypsin levels are normal

On day 10, her encephalopathy improved but she remained oliguric so hemodialysis was continued. She was also started on heparin in suspicion of hepatic vein thrombosis. Workup for thrombophilia (ANA, Anti-phospholipid antibody, Anticardiolipin antibody, Anti B2 glycoprotein, Protein C, Protein S, Antithrombin III, homocysteine) were negative. Gliadin IgA and tissue transglutaminase IgA levels are found to be within normal range. Serum protein electrophoresis showed no abnormal bands

Due to the possibility of Budd-Chiari syndrome, an upper GI endoscopy was done. It showed grade 1 varices in the lower third of the esophagus. There is mild diffuse inflammation throughout the entire stomach.

On day 14, a hepatic venogram was done which demonstrated complete thrombosis of the hepatic veins consistent with Budd Chiari syndrome. The orifice of the hepatic veins was unable to be catheterized despite multiple attempts. The flush cavogram demonstrated no unopacified blood entering the IVC from the liver. A single small collateral vessel was also identified arising from the posterior aspect of the cava with tiny branches measuring approximately 4-5 mm. The inability to access or recanalize the orifice of the hepatic veins precluded TIPS placement. So IVUS-guided DIPS was considered, which would require referral to a tertiary care center as the equipment to perform IVUS / DIPS was not available at our center.

The patient was planned for liver transplantation as it would be the better option in the setting of fulminant hepatic failure and on day 18, she was transferred to a higher center for liver transplantation

LAB VALUES	**PATIENT VALUES On admission**	**PATIENT VALUES on Day 5**
Total count	14400	306000
Neutrophils	75.7%	87.5%
Lymphocytes	13.9%	7.5%
Hemoglobin	16.6	16.2
Platelet count	725000	403000
BUN	15	35
Creatinine	1.14	3.65
Pro BNP	241	--
PT	15.5	21.3
INR	1.33	1.84
Total protein	6.4	5.7
Albumin	3.4	2.3
AST	63	329
ALT	74	697
Total bilirubin	2.2	2.1
Direct bilirbin	1.6	1.3

ASCITIC FLUID ANALYSIS	**RESULT**
Total count	233 cells
Neutrophils	71%
Lymphocytes	21%
Albumin	1.5 g/dl
Glucose	95 mg/dl
LDH	118

II. Discussion:

Budd Chiari syndrome is an uncommon disease affecting the liver in which there is obstruction to the hepatic venous outflow resulting in venous stasis and congestion causing hypoxic liver injury and hepatocyte necrosis. The obstruction to the hepatic outflow may be anywhere from the terminal hepatic venules to the junction of IVC and the right atrium. This syndrome was first described by a British internist, George Budd in 1845, the first pathological description of "obliterating endophlebitis of the hepatic veins" was given by Hans Chiari, an Australian pathologist in 1899. In chronic forms, hepatocyte necrosis is more prominent in centrilobular regions leading to centrilobular fibrosis finally causing cirrhosis of the liver. The most common risk factors for BD Chiari syndrome are myeloproliferative disorders followed by hypercoagulable states. A study by Alukal et al. showed that the hospitalization rate for Budd-Chiari syndrome increased from 4.96 per million population to 10.44 per million population in the US between 1998 and 2017. Also, it was found that there was associated cirrhosis in 18.7%, thrombosis of the portal vein in 7.9%, and thrombosis of the inferior vena cava in 6.4% of patients.[1]

The majority of patients present with classical features of abdominal pain, ascites, and hepatomegaly. The presentation may be acute, subacute, chronic, or rarely fulminant hepatic failure.[2] Our patient presented with ascites, pedal edema, and hepatomegaly with the initial symptoms starting before 2 weeks of presentation. Then she also developed renal failure, coagulopathy, and encephalopathy pointing to the diagnosis of acute hepatic failure.

Acute liver failure indicates severe liver injury with encephalopathy and impaired synthetic function (INR >/=1.5) developing in an individual without preexisting liver disease or cirrhosis in an illness less than 26 weeks duration. [3] The most common causes of acute liver failure are drug-induced hepatitis and viral hepatitis. The other causes include hypoxic/ischemic liver injury, veno-occlusive disease, acute Budd-Chiari syndrome, autoimmune hepatitis, Wilson disease, sepsis, HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome, acute fatty liver of pregnancy, mushroom ingestion, heatstroke, and malignant infiltration (with metastasis) of the liver. [4]

Drug-induced hepatotoxicity accounts for about 50% of cases of acute liver failure in the United States and is most commonly due to acetaminophen overdose. [5] Female sex, elderly age, malnourishment, alcohol use, and preexisting liver disease are the most common risk factors for Drug-induced liver injury. [6] Several other drugs are implicated in causing liver injury and they do so by either of the two mechanisms- the first one is predictable or intrinsic or dose-dependent and the other is unpredictable or idiosyncratic. The dose-dependent hepatotoxicity is classically due to acetaminophen. The majority of the drugs cause liver damage by idiosyncratic mechanisms. [7] Our patient had no history of hepatotoxic drug intake and her blood acetaminophen level was normal.

Toxins causing acute liver failure include, amanita phalloides mushroom toxin, cyanobacterial toxin, bacillus cereus toxin, yellow phosphorus, and organic solvents (carbon tetra chloride).

Hepatitis A and E are the most common viruses causing acute hepatic failure. Hepatitis B can also cause acute liver failure especially if immunocompromised/ on immunosuppressive therapy or coinfected with hepatitis C. Other viruses causing ALF are Ebstein-Barr virus, cytomegalovirus, adenovirus, herpes simplex, and varicella-zoster virus. [8] Our patient was evaluated for the viral etiology of hepatic failure and the viral panel turned out to be negative for the above viruses.

Wilson's disease can also present as acute liver failure in rare cases even though there is no family history. It presents with features of liver failure, neuropsychiatric features and hemolyticanemia. But our patient has no such features and her serum ceruloplasmin levels are normal ruling out the possibility of Wilson's disease. [9]

Sepsis-associated liver dysfunction can happen in early to severe sepsis presenting as elevated liver enzymes and hyperbilirubinemia. But our patient had no features of sepsis and her normal procalcitonin ruled out sepsis. It may also be due to liver ischemia caused by septic shock. [10]

Auto-immune hepatitis is a common cause of acute hepatitis and may present as acute liver failure. Acute auto-immune hepatitis can be subdivided into severe, non-severe, or fulminant forms. Among these, severe AIH can present as acute liver failure. Our patient was evaluated for auto-immune hepatitis by doing Serum total IgG, Anti-nuclear, anti-mitochondrial, Anti-smooth muscle, and anti-LKM-1 antibodies all of which turned out to be normal. Also, it is possible to have the autoimmune hepatitis profile negative in a few cases of autoimmune hepatitis which should be confirmed with liver histopathology [11] [12] [13]

The other most important cause of acute liver injury is the vascular causes including hepatic vein thrombosis and ischemic hepatitis due to severe systemic hypotension. Our patient had no hypotensive episodes severe enough to cause ischemic hepatitis. However, on evaluation, she was found to have thrombosis of the hepatic veins by MRI of the abdomen. Further hepatic venogram was done which confirmed the findings.

Budd-Chiari syndrome is a rare disorder in which there is an obstruction to the hepatic venous outflow leading to venous stasis and congestive hepatopathy. It can develop as acute or insidious and is classified into primary or secondary. The primary buddchiari syndrome is due to thrombosis or phlebitis of the hepatic veins, a venous process. In contrast, the secondary buddchiari syndrome is due to compression or invasion of the hepatic veins and /or the inferior vena cava by a lesion that arises outside the hepatic vein.

The presentation of Budd-Chiari syndrome may be acute, subacute, or chronic. The acute Budd-Chiari syndrome presents with intractable ascites and hepatic necrosis developing within a few weeks. The subacute form develops insidiously and presents with minimal ascites due to the development of venous collaterals. The chronic Budd-Chiari syndrome presents with cirrhosis and its complications. The common presentation may include jaundice, ascites, pedal edema, abdominal pain, hepatomegaly, liver failure, or hepatic failure.

BCS should always be suspected in a patient whenever there is:

1. Massive ascites with relatively normal liver functions
2. Sudden onset of ascites with painful hepatomegaly
3. Liver biopsy showing sinusoidal dilation in patients without heart disease
4. Fulminant hepatic failure along with hepatomegaly and ascites
5. Unexplained chronic liver disease
6. Liver disease with a thrombophilic disorder.

The most common risk factors for Budd-Chiari syndrome are myeloproliferative disorders, anti-phospholipid syndrome, Factor V Leiden mutation, protein C and protein S deficiency, anti-thrombin III

deficiency, hyperhomocysteinemia, oral contraceptives, and pregnancy. [14] The antiphospholipid antibody, anti b2 microglobulin antibody, anticardiolipin antibody, protein c and protein S level, antithrombin III level, serum homocysteine, Anti-nuclear antibody, peripheral smear, and imaging studies were all done and found to be negative.

The ascitic fluid analysis reveals elevated levels of protein (> 2 grams/dl), WBC counts <500 cells/mm3, and SAAG of <1.1 grams/dl in the chronic form.

The initial test of choice to confirm the diagnosis is the Doppler ultrasonogram. CT or MR imaging may be helpful if the Doppler ultrasonogram turns out to be equivocal or negative with a high index of suspicion.

The Doppler ultrasonography has high sensitivity and specificity in the detection of thrombosis of about 85-90%.

The ultrasound findings include,

1. The presence of inferior vena cava (IVC) thrombi and webs,
2. Decreased IVC diameter,
3. The presence of hepatic venous thrombosis,
4. Increased size of the caudate lobe,
5. Presence of ascites,
6. Presence of intrahepatic or extrahepatic collaterals,
7. Monophasic flow within the hepatic veins, and
8. remarkably high flow velocities in stenosed areas in the IVC or hepatic veins. [15] [16]

The sensitivity and specificity of MRI in detecting thrombosis is high about >90% and it becomes the most important non-invasive modality of investigation. [17] It can reveal the anatomy of the hepatic vasculature and also the presence of a portal venous collateral system to plan for the TIPS.

Hepatic venography can show the accurate site, the anatomy of the hepatic veins, and the severity of the obstruction but it is invasive in nature. The spider web pattern of the hepatic veins is the most common finding.

Liver biopsy often shows central venous congestion with areas of necrosis, and hemorrhage. Other findings include sinusoidal dilatation, thrombosis of terminal hepatic veins, and centrilobular liver cell atrophy and fibrosis. However, due to its invasive nature, it is not routinely employed for the diagnosis.

The management of BCS depends on the severity of the disease. Anti-coagulation, catheter-directed thrombolysis, TIPS, and Liver transplantation are the major treatment options for BCS. All patients with Budd-Chiari syndrome should be anti-coagulated irrespective of their symptoms as an underlying thrombophilic state is present in most cases. In the presence of ascites, it should be treated with diuretics and ascitic fluid paracentesis. Also, portal hypertension-related bleeding may need an endoscopic evaluation and treatment. [18]

Acute BCS may also be treated with Catheter-directed thrombolytic therapy, angioplasty, and stent placement. It should be done for patients with the acute form of BCS where angiography reveals a fresh thrombus. Thrombolysis can be done with Urokinase or tissue plasminogen activator infused through a catheter directly into the thrombosed hepatic vein. [19]

If the patient presents with a fulminant form of BCS, then they should be offered TIPS, and evaluation for liver transplant should also be done. The indications for TIPS include failed medical therapy, acute liver failure, and Rotterdam class III. [20] Patients with symptomatic ascites and gastrointestinal or variceal bleed should also be considered for TIPS. Pre-procedure jaundice and prior hepatic encephalopathy should not be considered as contraindications for TIPS in BCS.

Rotterdam score was determined with the equation as follows: [21]

(1.27 × encephalopathy) + (1.04 × ascites) + (0.72 × prothrombin time) + (0.004 × bilirubin).

Ascites and hepatic encephalopathy were scored as [1] present or [0] absent and prothrombin time as [1] higher or [0] lower than an INR of 2.3.

The patients were distinguished into three classes:

Class I (good prognosis) with a total score between 0 and 1.1;

Class II (intermediate prognosis) is between 1.1 and 1.5 and

Class III (poor prognosis) total score is higher than 1.5.

Our patient did not improve with early anticoagulation and also she developed acute liver failure hence she had a clear indication for performing TIPS. However, due to difficult anatomy and technical difficulties in performing the procedure, we could not perform TIPS for our patient.

Liver transplantation is indicated in cases of acute BCS with fulminant liver failure or in chronic BCS with decompensated cirrhosis. Our patient had features of liver failure and she also had failed medical management. Hence she was planned for liver transplantation for which she was referred to a higher center for liver transplant. [22]

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