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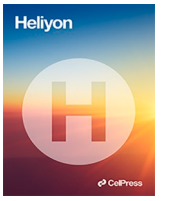

Case report

Acute liver failure as initial presentation in a Chinese patient with Budd-Chiari syndrome due to protein C deficiency: A case report and literature review

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ABSTRACT

Acute liver failure is an uncommon presentation in the clinic. Common causes for acute liver failure include viral hepatitis and drug-related hepatotoxicity. However, acute liver failure due to Budd-Chiari syndrome is rare. This case highlights the importance of necessary constrast-enhanced imaging studies to rule out vascular etiologies of acute liver failure, in addition to common causes like viral or drug-induced hepatic failure. We present a case of a male Chinese patient who presented with nausea, vomiting, fatigue, and fever after eating a large amount of fatty food. Six days after hospitalization, the patient developed acute liver failure and hepatic encephalopathy. Contrast-enhanced computerized tomography and ultrasound examinations revealed thromboses in the hepatic veins and inferior vena cava. Further testing also showed decreased protein C activity. Therefore, a diagnosis of Budd-Chiari syndrome secondary to protein C deficiency was made. He received supportive care and a transjugular intrahepatic portal shunt. Hepatic function, coagulation panel results, and clinical presentations gradually returned to normal. Budd-Chiari syndrome from protein C deficiency could be a rare but valid cause of acute liver failure in Chinese patients.

1. Introduction

Acute liver failure is an uncommon clinical presentation involving rapid loss of normal hepatocellular function [1], Without appropriate treatments, it carries a high mortality rate. Currently, acute liver failure accounts for approximately 8 % of all liver transplants, as per data from the Scientific Registry of Transplant Recipients (SRTR) and the European Liver Transplant Registry (ELTR) [2]. Acute liver failure from Budd-Chiari syndrome (BCS) is an extremely rare condition, accounting for <1 % of patients in the Acute Liver Failure Study Group registry in the United States [3]. BCS refers to an uncommon heterogenous group of disorders with hepatic venous outflow blockage due to stenosis or obstruction in the central veins of the hepatic lobule, the main trunk of the hepatic vein, and the adjacent inferior vena cava [4]. The obstruction can not only cause portal hypertension and ascites, but also lead to

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Abbreviations

(BCS) Budd-Chiari syndrome
(CT) computerized tomography
(SAAG) serum-ascites albumin gradient
(HPF) High Power Field
(DSA) digital subtraction angiography
(PAI-1) inactivate plasminogen activation inhibitor-1
(t-PA) tissue plasminogen activator
(PROC) Protein C
(TIPS) Transjugular intrahepatic portal shunt

decreased blood supply to the liver and hepatic necrosis, which can ultimately lead to the deterioration of hepatic function. Most patients with BCS have subacute presentation due to the formation of collateral circulation [5]. The most common underlying cause for venous blockage in BCS is thrombosis due to a hypercoagulable state, such as myeloproliferative disorders, malignancy, oral contraceptives, factor V Leiden deficiency, and protein C deficiency [6]. Protein C deficiency is a rare disorder [7,8], and acute liver failure due to BCS that is caused by protein C deficiency is extremely rare. There have been limited studies to investigate protein C deficiency in Chinese BCS patients [9]. Herein, we present a case to describe a Chinese acute liver failure patient with BCS secondary to protein C deficiency.

2. Case presentation

A male patient presented to the local hospital due to nausea, vomiting, fatigue, and fever as high as 38.4 °C. He had consumed a large amount of meat and eggs two days earlier. An abdominal ultrasound revealed massive ascites. He underwent a paracentesis procedure and was then transferred to our hospital. At hospital admission, his vital signs were stable. He was awake and alert, but in acute distress. On physical examination, his abdomen was noted to be distended with shifting dullness, tender to palpation in the right lower quadrant, notably no rebound tenderness or abdominal wall rigidity was appreciated. Cardiopulmonary and neurological examinations were normal. The patient had a medical history of fatty liver but denied any history of hypertension, diabetes, coronary artery disease, viral hepatitis, or smoking. He also denied any medication intake or occasional drinking. The laboratory tests revealed abnormal hepatic function (Table 1), white blood cellcount of 19.9 × 10^9/L, neutrophil percentage of 80 %, hemoglobin levels of 181 g/L, and a platelet count of 117 × 10^9/L. Coagulation tests showed a prothrombin time of 25.1 sec, prothrombin activity of 31 %, and an international normalized ratio of 2.27. The blood chemistry panel showed creatinine at 109.1 μmol/L, urine nitrogen at 11.9 mmol/L, procalcitonin at 2.2 ng/L, and hypersensitive C-reactive protein at 79.6 mg/L. An abdominal computerized tomography (CT) scan revealed an enlarged liver with heterogeneously decreased signals and ascites. The diagnosis of acute liver failure (model for end-stage liver disease score 20) was made based on the patient's medical history, physical examination, elevated bilirubin, and abnormal coagulation panel.

Subsequently, the laboratory tests revealed that protein C activity was at 31 % (normal range 70–140 %) and protein S activity was at 93.4 % (normal range 63.5–149 %). Ascitic fluid analysis indicated only transudate, with no cancer cells identified. The serum-ascites albumin gradient (SAAG) of abdominal fluid was 2.00 g/dL. The ascites culture was negative. Tests for Epstein-Barr virus, cytomegalovirus, and hemorrhagic fever antibodies were all negative. Viral hepatitis antibodies, antinuclear antibodies, anticardiolipin antibodies, and lupus anticoagulant levels were within normal limits. Triple-phase contrast-enhanced CT of the abdomen showed morphological liver changes, hepatic S2 hemangioma, and thromboses in the inferior vena cava and three hepatic veins (Fig. 1 (A,B)). Acoustic contrast of viscera examination revealed thromboses in the left hepatic vein and middle hepatic vein, with unclear

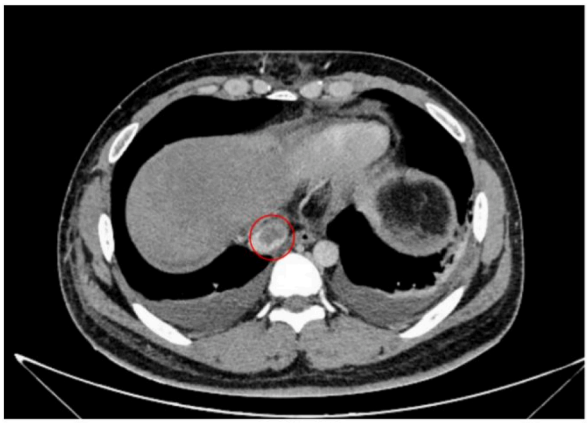
Table 1
Dynamic changes of the hepatic function tests.

Hepatic function tests	Day 1 (hospital admission)	Day 11 (after hepatic vein recanalization and heparin and aspirin therapy)	Two months later (TIPS)	Clinic follow-up at six months	Reference range
Aspartate aminotransferase, U/L	3196.2	90.8	17.9	28.1	15.0–40.0
Alanine aminotransferase, U/L	2293.7	59.1	16.0	23.9	9.0–60.0
Albumin, g/L	32.1	28.9	25.3	47.4	40.0–56.0
Bilirubin, μmol/L					
Total	45.9	132.7	27.3	16.2	0.0–26.0
Direct	20.6	52.7	10.9	2.8	0.0–6.8
Indirect	28.5	79.7	16.4	13.4	5.0–20.0

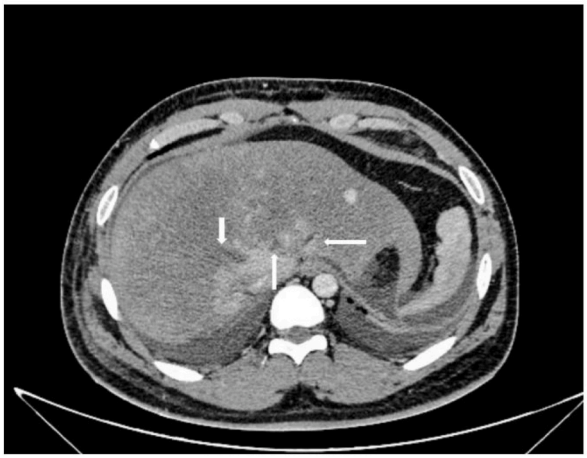
TIPS, transjugular intrahepatic portal shunt.

images in the right hepatic vein (Fig. 2). The BCS was diagnosed.

On the fifth day, the patient looked lethargic with a blood ammonia level of 100 μmol/L. A diagnosis of hepatic encephalopathy was considered. During the percutaneous inferior cavity vein and hepatic vein imaging study on the sixth day, the distal hepatic vein looked congested with no blood flow. There was a filling defect at the location where the inferior vena cava entered the right atrium. Recanalization was successful in the hepatic vein entering into the inferior vena cava and the heart, but failed in the hepatic vein entering into the inferior vena cava. He then received low molecular weight heparin together with aspirin. On the 11th day, repeat hepatic function tests showed significant improvements in liver transaminases but not bilirubin levels (Table 1). He had epistaxis that was controlled after compression. The patient's urine looked dark, and a stool guaiac test was positive for occult blood. Urinalysis showed a red blood cell count of 1067.10/μL and was negative for urine bilirubin, with a microscopic red blood cell count of 192.1/HPF. Anticoagulant therapy was continued as the hemoglobin was still in the normal range. On the 39th day, in order to further define the classification of Budd-Chiari syndrome and to attempt recanalization, the patient underwent digital subtraction angiography (DSA). Contrast agent was only shown in the distal branches of the hepatic vein, but not the main trunk of the left, middle, or right hepatic veins. There was compensatory blood return in the portal vein. During the surgery, an ultrasound-guided liver puncture was performed. On the 44th day, the pathological examination revealed obviously dilated and congested hepatic sinusoids with surrounding atrophic hepatic hilum and a disappearance of hepatocytes (Fig. 3). Two months later, the patient received a transjugular intrahepatic portal shunt. The postoperative follow-up examinations revealed that the hepatic function (Table 1), coagulation panel, and routine blood test results were normal. At the clinic visit six months later, the repeated laboratory tests showed normal hepatic functions (Table 1). In addition, the routine blood test showed a leukocyte count of 8.1 × 10^9/L, neutrophil percentage of 66 %, hemoglobin 135 g/L, platelet count 309 × 10^9/L. Coagulation test showed prothrombin time 18.9 seconds, prothrombin activity 84



A



B

Fig. 1. Thrombosis in the inferior vena cava (**A**, red circle, 146 × 104 mm) and hepatic veins (**B**, white arrows; left, middle, and right hepatic veins from the left to the right, 145 × 113 mm). (144 × 144 DPI). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

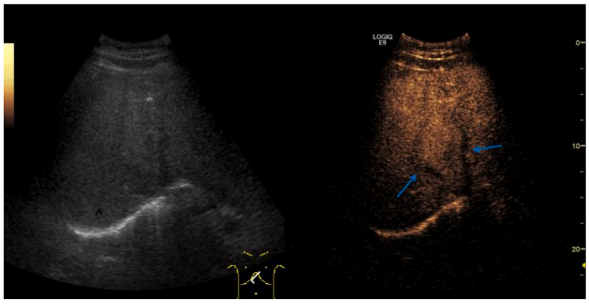


Fig. 2. Acoustic contrast of viscera. No contrast agent seen in the left hepatic vein (left arrow) or middle hepatic vein (right arrow) in the arterial phase, portal phase, or delayed phase. 120 × 65 mm (144 × 144 DPI).

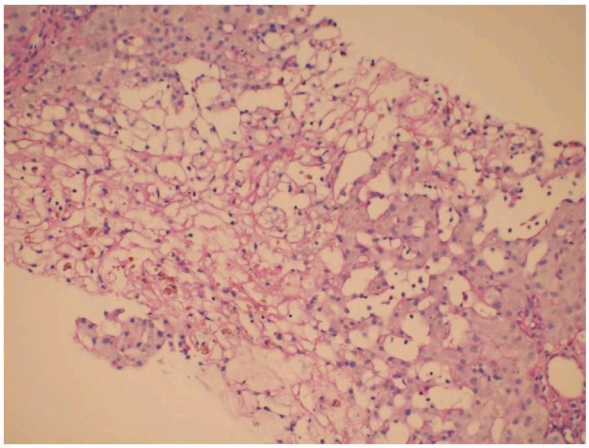


Fig. 3. Liver biopsy specimen revealed dilated and congested hepatic sinusoids with surrounding atrophic hepatic hilum and disappearance of hepatocytes.

%, international normalized ratio 1.09. The blood chemistry panel showed creatinine 70.5 μmol/L, urea nitrogen 6.2 mmol/L, procalcitonin 0.1 ng/L, and hypersensitive C-reactive protein 2.6 mg/L.

3. Discussion

The patient in the current study initially presented with gastrointestinal symptoms and general malaise, but he rapidly developed hepatic encephalopathy within seven days. There was also no evidence of autoimmune disease, or anticardiolipin antibody syndrome. Considering the thrombosis present in the hepatic veins and inferior vena cava in the contrast-enhanced abdominal CT and contrast-enhanced ultrasound examinations, the diagnosis of BCS was confirmed. The patient had reduced protein C activity, and was not on anticoagulant drugs, such as warfarin, that could affect protein C synthesis. Protein S levels were normal, which suggested the synthetic function of the liver was not severely impaired and likely did not contribute to the decreased protein C level. Our patient had clinical presentations consistent with heterozygous protein C deficiency, including adult onset at a relatively young age and no other explanation for the venous thrombosis formation. Unfortunately, we were not able to perform a genetic study in this case. A detailed genetic study on the patient and close family members could further explore the underlying disease etiology and might help to prevent thromboembolic events in potential patients.

The etiology of BCS can be classified into primary and secondary causes. The latter includes myeloproliferative diseases, paroxysmal nocturnal hemoglobinuria, pregnancy, oral contraceptives, antiphospholipid antibody syndrome, Behçet's disease, and malignancy [6]. The primary causes are mainly due to inherited hypercoagulable states, such as protein C deficiency, protein S deficiency, antithrombin deficiency, and coagulation factor V gene Leiden mutation. Among them, protein C deficiency is one of the high-risk factors for thrombotic diseases. Protein C is a serine protease synthesized in the liver that can be activated by thrombin. Activated protein C can inhibit factor V activation, inactivate plasminogen activation inhibitor-1 (PAI-1), and promote fibrinolysis by inducing the release of tissue plasminogen activator (t-PA). Protein C deficiency can be hereditary or acquired [10]. Hereditary protein C deficiency is caused by mutations in the PROC gene. The incidences of homozygous and heterozygous mutations were approximately 1 in 5 million to 1 in 7.5 million and 1 in 200 to 1 in 500, respectively [11]. Studies in China suggested that hereditary antithrombin, protein C and protein S deficiency were important risk factors for venous thromboembolism in Chinese patients with BCS [9,14].

Therefore, Chinese BCS patients should receive appropriate tests to rule out these etiologies.

Most patients with BCS have sub-acute disease onset, and BCS causing acute liver failure has been rarely reported in the clinic [5], but acute liver failure could develop within a few weeks in BCS patients [13]. In a retrospective study of 1237 patients with acute liver failure, the most common cause of acute liver failure was drug overdose, BCS caused only 1.5 % of liver failure, although it had a higher mortality rate [12]. In a study of 19 BCS patients complicated by acute liver failure, only 11 patients survived after three weeks of treatment [3]. In the present case presentation, our patient first received the intermittent anticoagulation after the hospital admission. Although transaminase and bilirubin level gradually decreased, his blood coagulation function and low serum albumin level did not improve. Interventional procedure was attempted twice to recanalize the obstruction in the hepatic vein, but with unsuccessful outcomes. This suggested an alternative treatment, such as transjugular intrahepatic portal vein bypass or liver transplantation, should be considered. Finally, he received a transjugular intrahepatic portal shunt. We did not perform the angioplasty since the digital subtraction angiography did not show clear images in the main trunks of the left, right, or middle hepatic veins. After the transjugular intrahepatic portal shunt, the patient's hepatic function, coagulation panel, electrolytes, and routine blood test results returned to within normal limits. The electrolyte imbalance was also corrected. Currently, this patient was followed up routinely in the clinic.

In patients with acute liver failure with unknown causes, clinicians should perform necessary imaging tests, such as ultrasound or contrast-enhanced CT scan, to rule out BCS. Once BCS diagnosis is confirmed, anticoagulation, stenting, or shunt placement should be provided [3]. During the treatment process, laboratory hepatic functions and clinical signs of hepatic encephalopathy should be monitored. The etiology of BCS, such as myeloproliferative disorders, malignancy, factor V Leiden deficiency, or protein C deficiency, should be explored. These patients should be closely followed up in the clinic for repeated physical examination, as well as hepatic function and coagulation panel tests. Some patients may require lifelong anticoagulant therapy. More research is needed.

4. Limitations

The single-sample nature of this case report study, short follow-up period, and the rarity of this illness require additional research evidence to further improve our understanding of this type of disease.

5. Conclusion

Acute liver failure could be a rare clinical presentation of BCS, and protein C deficiency could be the cause for BCS in Chinese patients. This case highlights the importance of necessary contrast-enhanced imaging studies to rule out vascular etiologies of acute liver failure, in addition to common causes like viral/drug-induced hepatic failure. Once BCS is diagnosed, the underlying etiology should be further explored to determine the best treatment option and long-term follow up plan for the patient.

Ethics statement

This study was reviewed and approved by the Institutional Review Board and Ethics Committee of the First Hospital of Jilin University, with the approval number AF-IRB-032-06. The patient provided written informed consent for the publication of this case report and images.

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Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Data availability statement

Research-related data are not stored in publicly available repositories. Data are included in the article and related references and supplementary materials.

CRediT authorship contribution statement

Wanling Xu: Writing – original draft, Data curation. **Wenjing Tang:** Writing – original draft, Data curation. **Weiying Yang:** Validation, Resources, Investigation. **Lichao Sun:** Writing – original draft, Data curation. **Wei Li:** Supervision, Project administration. **Shouqing Wang:** Validation, Investigation. **Xiuxian Zang:** Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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