



Hepatic Necrosis Mimicking Infiltrative Masses in Acute Budd-Chiari Syndrome With Hereditary Protein C Deficiency

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ABSTRACT

We report the case of a patient with an unusual acute Budd-Chiari syndrome (BCS). The patient presented with high-grade fever and right upper quadrant pain. Infiltrative lesions at the right hepatic lobe and segment IVB with intrahepatic inferior vena cava and right hepatic vein thrombus appeared on abdominal imaging. Liver biopsy revealed hepatic infarction compatible with acute BCS. Thrombophilia work-up demonstrated low protein C activity with the -1657C/T mutation of the *PROC* gene. Necrotic liver mass with acute BCS related to congenital protein C deficiency was diagnosed. Patient symptoms and necrotic masses improved after anticoagulant treatment for 4 months.

INTRODUCTION

Budd-Chiari syndrome (BCS) results from the hepatic venous outflow obstruction, independent of the cause or level of obstruction.¹ The typical presentation of acute BCS is abdominal pain, ascites, hepatomegaly, and dilated superficial abdominal vein.¹ BCS divides into “primary BCS,” which contributes to vascular disease and “secondary BCS” associated with the external compression or invasion of the inferior vena cava (IVC) or hepatic veins (HVs).² The important risk factors of BCS are myeloproliferative disease, oral contraceptive pills, and hereditary thrombophilia.²

CASE REPORT

A 16-year-old Thai boy presented with right upper quadrant abdominal pain and high-grade fever for 3 weeks. He was previously healthy and not receiving any medication. He reported a history of embolic stroke in his father and grandmother. Physical examination revealed a body temperature of 38.5°C without jaundice or any stigmata of chronic liver disease. There was tenderness at the right upper quadrant area and hepatomegaly with a liver span of 16 cm. No splenomegaly was observed, and the platelet count was $129,000 \times 10^3/\mu\text{L}$. Liver function test (LFT) showed total bilirubin 1.3 mg/dL, direct bilirubin 0.8 mg/dL, aspartate aminotransferase 125 IU/L, alanine aminotransferase 132 IU/L, and alkaline phosphatase 79 IU/L. Serum levels of carbohydrate antigen 19-9 and alpha-fetoprotein were normal at <2.0 and 1.22 IU/mL, respectively.

Contrast-enhanced abdominal computer tomography revealed multiple ill-defined infiltrative hypodense lesions with progressive delayed enhancement involving the entire right hepatic lobe and segment IVB with intrahepatic IVC and right HV thrombosis (Figure 1). Portal vein and hepatic artery were patent. BCS with liver abscess or infiltrative cholangiocarcinoma was initially diagnosed. Ultrasound-guided biopsy of the liver mass demonstrated hepatic atrophy at zone 3 of the hepatic lobule compatible with hepatic infarction (Figure 2). No definite malignancy, inflammation, or hemorrhage was visible on histopathology. Evaluation for thrombophilia was performed and revealed low protein C activity with 53 U/dL (normal: 70–140 U/dL). Subsequently, the

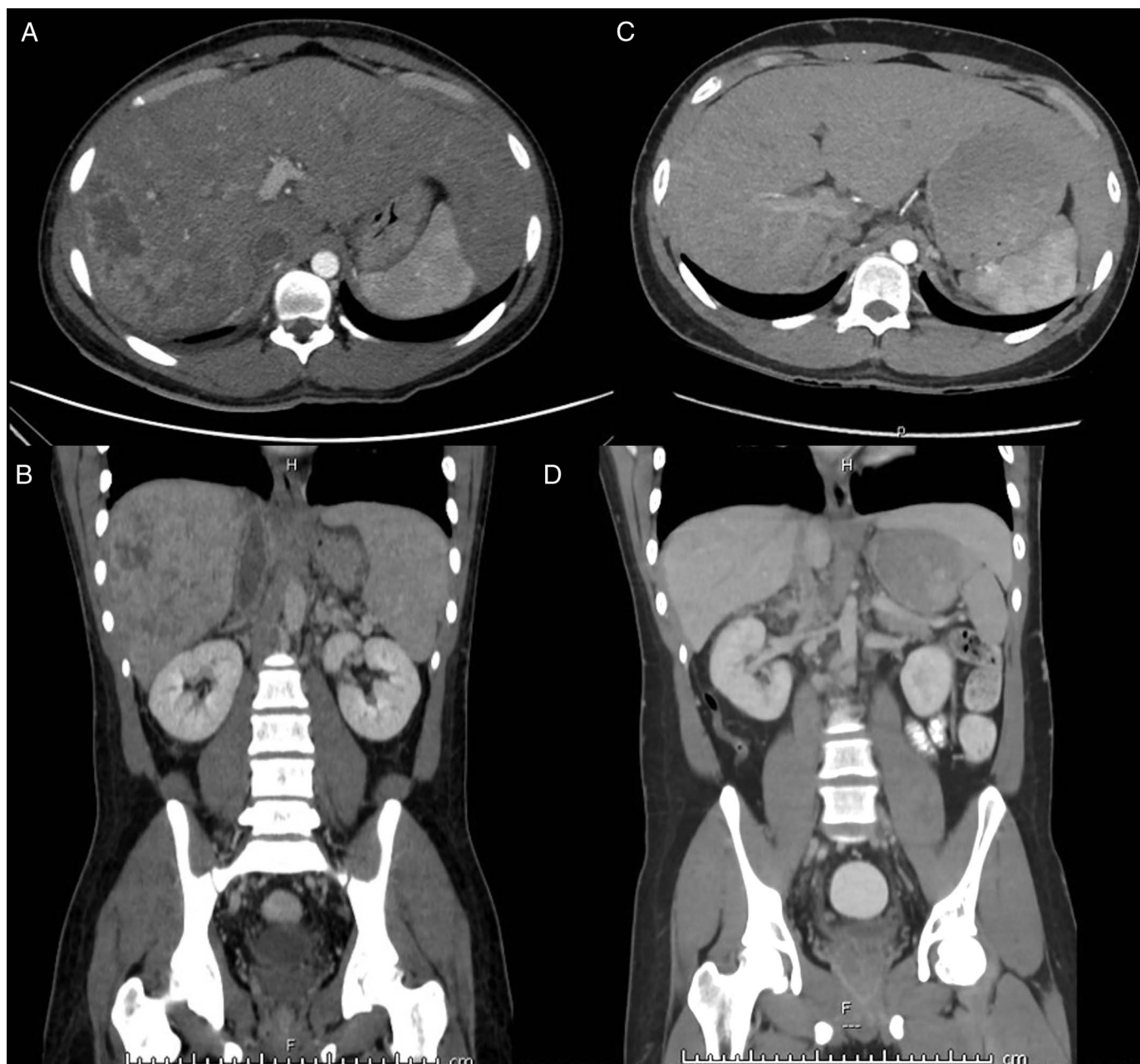


Figure 1. Contrast-enhanced abdominal computed tomography (CT) revealed an ill-defined infiltrative hypodense lesion with progressive delayed enhancement at the right hepatic lobe (A) on arterial phase with the extension of the thrombus to the inferior vena cava (IVC) (B). Follow-up abdominal CT after 4 months of anticoagulant revealed resolution of the infiltrative lesion in the right hepatic lobe on arterial phase (C) and reduction of thrombus size in IVC and right HV (D).

heterozygous -1657C/T mutation in exon 1 of the *PROC* gene was identified. The *JAK2* V617F mutation was negative in our case. Necrotic liver mass-related BCS with hereditary protein C deficiency was diagnosed. The patient was treated with low-molecular-weight heparin (LMWH) 1 mg/kg (60 mg) twice daily.

On the seventh day of admission, he developed acute dyspnea and shock, requiring an inotropic drug. Chest x-rays revealed bilateral cephalization and cardiomegaly consistent

with pulmonary congestion. An echocardiogram showed severely impaired left ventricular systolic function with left ventricular ejection fraction 16% and severe global wall hypokinesia. Coronary artery angiography was performed and demonstrated normal coronary arteries. Cardiac magnetic resonance imaging (MRI), however, revealed evidence of transmural myocardial necrosis along the mid-distal right coronary artery and subendocardial necrosis along the left circumflex artery. Ischemic cardiomyopathy from coronary thrombosis was likely the diagnosis.

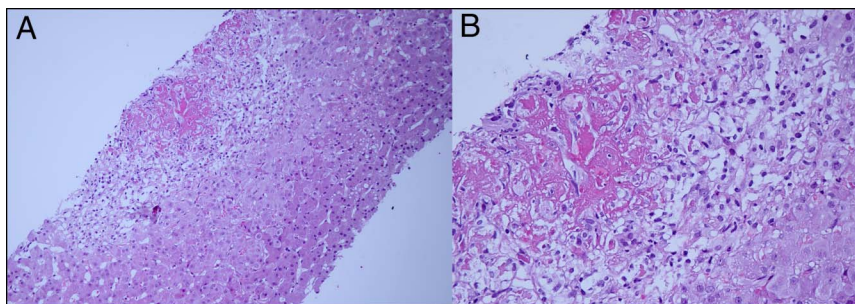


Figure 2. Liver biopsy of the hepatic lesion at right hepatic lobe revealed hepatic infarction at zone 3 of hepatic lobule on 4× magnification (A) and hepatic atrophy surrounding the central vein on 10× magnification (B).

Experts recommend lifelong anticoagulation in patients with BCS. However, there is no randomized controlled study to support the selection of a preferred regimen.³ Our patient was initially managed with LMWH and subsequently switched to a lifelong oral vitamin K antagonist. After 4 months of anticoagulant treatment, follow-up imaging revealed improved hepatic infarction and thrombus in IVC and right HV (Figure 1). Apart from improved imaging, the LFT was improved with total bilirubin 1.52 mg/dL, direct bilirubin 0.53 mg/dL, aspartate aminotransferase 16 IU/L, alanine aminotransferase 16 IU/L, and alkaline phosphatase 63 IU/L.

DISCUSSION

To the best of our knowledge, only 3 cases of the necrotic hepatic mass presenting with acute BCS have been reported.⁴⁻⁶ Extensive hepatic hemorrhage and necrosis in BCS can lead to multiple hypodense areas with patchy enhancement in computed tomography/MRI mimicking infiltrative mass. The differential diagnosis of liver mass-related BCS may include malignancy, regenerative nodule, and focal nodular hyperplasia. Therefore, a biopsy of hepatic mass with an uncertain diagnosis is necessary.⁴ The mechanism of hepatic necrosis in BCS is due to thrombosis or obstruction of hepatic venous outflow, resulting in increased sinusoidal pressure, which can cause ischemic necrosis of hepatocytes. The peripheral parts of the liver are more affected by venous obstruction than the central parts. Our patient showed lesions predominantly at the right hepatic lobe because of the extension of the thrombus into the right HV.

Up to 87% of patients with BCS carry risk factors for thrombosis including myeloproliferative diseases, Factor V Leiden mutation, protein C deficiency, protein S deficiency, and anti-thrombin deficiency.² Hereditary protein C deficiency is not a common risk factor. The prevalence of inherited protein C deficiency among patients with BCS was 3.8%.⁷ The protein C deficiency was defined as low protein C activity with low or normal antigen level. Decreased protein C level might be the result of severe liver dysfunction.¹ Testing of *PROC* gene's mutation is helpful to confirm the diagnosis of congenital protein C deficiency.⁸

Our case represented necrotic liver masses with acute BCS associated with congenital protein C deficiency. Genetic analysis revealed a heterozygous -1657C/T mutation in exon 1 of the *PROC* gene. The association between -1657C/T mutation (rs1799808) in *PROC* gene and protein C deficiency has been previously reported in the Thai population.⁹ Patient's first-degree family members were advised to evaluate protein C gene mutation. Only 1 previous case report with BCS has completed a genetic analysis. That case was a 34-year-old Japanese woman who presented with bilateral leg edema, and an abdominal MRI showed thrombus in IVC. She was diagnosed with BCS. Reduction of protein C activity and C.125C > A Arg42Ser mutation of *PROC* gene were identified in this patient and her father and younger brother.¹⁰

The first-line treatment of BCS is an anticoagulant that prevents further thrombus accumulation and facilitates recanalization of the hepatic venous outflow tract.¹ Previous research has shown that 10%-20% of patients with BCS responded to anticoagulants within 2-5 months.^{11,12} Additional therapies including thrombolysis and angioplasty are used in patients who do not respond to the anticoagulant.¹ Our patient was initially treated with LMWH; however, local thrombolysis and mechanical angioplasty were not performed because of infeasible technique and long-length thrombosis. In patients with protein C deficiency and BCS, lifelong maintenance was currently recommended; however, the choice of anticoagulant was controversial because of the lack of a supported randomized control study.³ LMWH was changed to lifelong vitamin K antagonist in our patients. After 4 months of anticoagulant treatment, follow-up imaging revealed improved hepatic infarction and thrombus in IVC and right HV.

DISCLOSURES

Author contributions: P. Ananchuensook wrote the manuscript. J. Karuehardsuan, A. Sanpawat, and N. Wisedopas provided the pathology images. P. Komolmit and K. Thanapirom revised the manuscript. K. Thanapirom is the article guarantor. All authors reviewed and approved the final version of the manuscript.

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