Budd-Chiari syndrome: a rare and life-threatening complication of Crohn’s disease

Camila C Simoes,1 Yezaz A Ghouri,2 Shehzad N Merwat,2 Heather L Stevenson1

CASE REPORT

SUMMARY
Budd-Chiari syndrome (BCS) is characterised by obstruction of hepatic venous outflow and may be triggered by the prothrombotic state associated with inflammatory bowel disease (IBD). We reported a case of Crohn’s disease (CD) that presented with anasarca, ascites, symptomatic hepatomegaly, elevated liver enzymes, increased prothrombin time and low albumin. Oesophagogastroduodenoscopy and colonoscopy confirmed active CD. Abdominal CT showed hepatic vein thrombosis. Liver biopsy revealed severe perivenular sinusoidal dilation with areas of hepatocyte dropout, bands of hepatocyte atrophy and centrilobular fibrosis, suggestive of BCS. The patient was treated with steroids for CD and systemic anticoagulants for BCS. His liver function and enzymes normalised, and he reported symptomatic improvement. The precise mechanism responsible for increased hypercoagulability in IBD remains unclear. Early recognition and treatment for possible thrombotic complications of CD is critical to prevent potentially fatal events like pulmonary embolism or liver failure.

BACKGROUND
Crohn’s disease (CD) is a type of inflammatory bowel disease (IBD) that can involve any part of the gastrointestinal tract. It causes a systemic inflammatory state that can involve the joints, eyes, liver, skin and haematological system. Generally, the systemic inflammatory response consists of fevers, chills, night sweats, myalgias and chronic fatigue. Elevation of acute phase reactants like the erythrocyte sedimentation rate and C reactive protein can also be observed. Common complications are gastrointestinal (GI) stricture and fistula formation, perforation, haemorrhage, malabsorption and hypercoagulability. The disease may induce a prothrombotic state leading to occlusion in both arteries and veins. Thrombosis have been reported to occur in hepatic veins, portal veins and in the inferior vena cava (IVC).1 Hepatic venous outflow obstruction is the underlying cause of Budd-Chiari syndrome (BCS), classically presenting with a clinical triad of abdominal pain, ascites and hepatomegaly. CD as a precipitant of BCS, although recognised, is extremely rare and there have been few reported cases.2–5 Here, we are presenting a unique case of BCS in a patient with CD who concomitantly developed hepatic vein and IVC thrombosis leading to the development of cirrhosis and showed substantial improvement with treatment.

CASE PRESENTATION
A 27-year-old African-American man was admitted to our institution as a transfer from an outside hospital to receive a higher level of care due to new-onset ascites and bilateral lower extremity oedema for the previous 2 weeks. He had a history of intermittent abdominal pain, haematochezia and diarrhoea for the past year, when he was diagnosed with IBD at an outside hospital. At that time, he was prescribed mesalamine and steroids, which he took for a short period with improvement in his diarrhoea although he never achieved complete remission. Due to the cost of the medications, he discontinued them and was lost to follow-up for approximately 6 months. On admission, he complained of new onset of dyspnoea on exertion, fatigue and abdominal swelling. He had developed severe bloody diarrhoea over the last 1 month, suggestive of an acute flare in the setting of chronically uncontrolled disease. His physical examination revealed an alert and oriented individual with pale conjunctiva and no signs of icterus. He had prominent tachycardia (heart rate 124/min), bilateral pitting pedal oedema and a distended abdomen with the presence of shifting dullness, suggestive of ascites. The remainder of his physical examination was normal with no changes noted on the skin and he had intact arterial pulses in all four extremities.

INVESTIGATIONS
Laboratory studies determined that he had iron deficiency anaemia (haemoglobin 5.7 g/dL, mean corpuscular volume 57 fl, undetectable serum iron and ferritin of 9 mg/dL) from chronic gastrointestinal blood loss, normal bilirubin (total: 0.8 mg/dL and unconjugated: 0.4 mg/dL) and creatinine (0.6 mg/dL) levels, increased prothrombin time (16.6 s), hypoalbuminaemia (2.2 g/dL) and elevated liver enzymes (alkaline phosphatase: 138 U/L; alanine transaminase: 83 U/L; aspartate transaminase: 81 U/L). Stool examination revealed positive faecal leucocytes but was otherwise negative for faecal culture for enteric pathogens including Clostridium difficile toxin, Giardia antigen, Cryptosporidium antigen and other ova and parasites. The elevation of his liver enzymes remained unexplained, as he had no history of alcohol abuse and serological studies for hepatotropic viruses were negative. Laboratory studies performed to evaluate for Wilson’s disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, non-alcoholic steatohepatitis and primary biliary cholangitis were also negative.

1Department of Pathology, University of Texas Medical Branch, Galveston, Texas, USA
2Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, USA

Correspondence to
Dr Heather L Stevenson,
hlsteven@utmb.edu

CCS and YAG contributed equally.

Accepted 28 December 2017

To cite: Simoes CC, Ghouri YA, Merwat SN, et al. BMJ Case Rep Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222946
Abdominal ultrasound showed hepatomegaly with moderate ascites. Ascitic fluid was sampled which showed <250 neutrophils and serum ascites albumin gradient of >1.1 consistent with portal hypertension. Oesophagogastroduodenoscopy and colonoscopy to further evaluate his bleeding and history of IBD were performed. Oesophagogastroduodenoscopy revealed erethyma in the antrum of stomach and multiple superficial duodenal ulcers (figure 1). Biopsies from the upper and lower GI tract showed gastrroduodenitis, a granula in the stomach (figure 2) and terminal ileitis. Colonoscopy revealed prominent ulceration in terminal ileum and caecum with few areas of erythema in the rest of colon. Based on these features, including the endoscopic appearance and histology findings, a diagnosis of CD was made. He underwent abdominal CT scan, which showed evidence of thrombi in the hepatic vein, IVC and portal vein; hepatomegaly with areas of liver injury and relative sparing of caudate lobe and large volume ascites (figure 3). A transcutaneous liver biopsy was obtained which showed stage 4, primarily centizonal fibrosis, with partially obliterated central veins, areas of hepatocyte dropout and clusters of perivenular haemosiderin-laden macrophages (figure 4). The histopathological features were consistent with hepatic cirrhosis due to BCS. Except for the liver fibrosis, no other extraintestinal manifestations of CD were present.

**TREATMENT**

The patient was transfused with packed red blood cells for his symptomatic anaemia and started on oral prednisone and a low dose of 20 mg intravenous furosemide every 12 hours for 2 days followed by oral spironolactone and furosemide for his CD and anasarca, respectively. To prevent detrimental changes in osmolality, no albumin infusion was given to the patient, since he had already received multiple packed red blood cell transfusions which raises serum osmolality.

He was also started on heparin intravenous infusion and then transitioned to oral apixaban for long-term anticoagulation therapy. He was not evaluated for an underlying hypercoagulable state during his illness due to financial constraints and his uninsured status.

**OUTCOME AND FOLLOW-UP**

Eventually the patient’s clinical status improved and he was discharged. He was followed up in clinic and was started on azathioprine and sulfasalazine with a plan to slowly taper his steroids. This was followed by initiation of adalimumab therapy. During his sequential follow-up visits, his abdominal pain improved, GI bleeding was absent, bowel movements were reduced to about two per day, he gained 10 kg of weight, lower extremity swelling resolved and abdominal distension nearly normalised.

**DISCUSSION**

The incidence of IBD has increased dramatically during the last four decades, with approximately 5 million individuals affected in North America and Europe. Although IBD primarily affects the bowel, there are many known secondary effects on patients with IBD that are now widely accepted, including an increased risk of venous thromboembolic events, liver disease, cancer and bone disease. Thrombosis in IBD is characterised by both systemic venous thromboembolic events and focal microthrombi in the vasculature of the inflamed intestine. There are 8–10

---

**Figure 1** Endoscopic image of second portion of duodenum showing multiple superficial ulcers with mucosal erythema.

**Figure 2** (A) Gastric mucosal biopsy showing non-necrotising granulomatous lymphocytic inflammation in a background of chronic active gastritis, consistent with the patient’s diagnosis of Crohn’s disease (CD) (H&E stain, ×20 magnification). (B) Duodenal biopsies showing extensive neutrophilic and lymphocytic inflammation extending beyond the muscularis mucosa, consistent with the patient’s diagnosis of CD (H&E stain, ×20 magnification). The terminal ileum and colon also showed patchy areas of cryptitis, architectural distortion and granulation tissue (images not shown).
several proposed aetiologies for this increased risk, including thrombocytosis and platelet activation, hyperhomocysteinaemia, increased fibrinogen, impaired fibrinolysis, autoantibodies, elevated procoagulation factors and/or decreased anticoagulation factors and procoagulation mutations, yet no consensus has emerged.

The portal venous system drains blood to the liver from majority of the gastrointestinal tract (except the anus), spleen, pancreas and gall bladder. The superior and inferior mesenteric veins join the splenic vein to form the portal vein which carries blood to the liver. The blood from the liver is drained by the hepatic veins into the IVC. BCS can be characterised as any pathophysiological process that results in interruption or diminution of the normal blood flow out of the liver, either within the hepatic veins or IVC. The occlusion in the extrahepatic venous system may on occasion, cause portal vein thrombosis. There is considerable overlap in the aetiology and clinical management of patients with BCS and portal vein thrombosis. Venous obstruction in the liver is distributed in the following frequencies of incidence: 62% in the hepatic veins, 7% in the IVC, 31% involving both and 14% within the portal vein. Symptomatic patients with BCS typically present with ascites, abdominal pain, hepatomegaly and in some cases hepatic necrosis leading to acute liver failure. BCS leads to hepatic congestion, portal hypertension, ascites, oesophageal varices and eventually cirrhosis. It can be classified as acute, subacute or chronic. An underlying disorder can be identified in over 80% of cases, with myeloproliferative disorder being the most common cause of acquired BCS.

The risk of developing BCS in patients with CD is higher during IBD ‘flares’. Individuals with IBD have a threefold to fourfold increased risk of developing venous thromboembolic events. Notably, several studies have demonstrated that proinflammatory cytokines can counteract natural anticoagulant activity leading to a hypercoagulable state. The diagnosis of CD usually precedes or occurs simultaneously with the diagnosis of BCS.

In our patient, CD was diagnosed more than 1 year before the diagnosis of BCS. CD can lead to thrombosis of critical areas like

Figure 3  CT scan of abdomen and pelvis. (A) Coronal view showing thrombosis in the common hepatic vein (red arrow) and a partially occluding thrombus in the inferior vena cava (yellow arrow). The diseased ileum in the lower abdominal quadrant is marked with an arrow head. (B) Transverse view showing diffuse hepatic parenchymal injury with sparing of the caudate lobe.

Figure 4  (A) The patient’s liver biopsy showed extensive perivenular sinusoidal dilation, bands of hepatocyte atrophy, haemosiderin deposition (primarily within macrophages); (B), areas of hepatocyte dropout and occasional occlusion of central veins (B, arrow). (C) A Masson’s trichrome stain showed central veins (arrow) with prominent centrinzonal fibrosis, diffuse subsinusoidal fibrosis and areas of bridging.
the dural venous system in the brain or the pulmonary vasculature, which can lead to life-threatening outcomes.4–5 Furthermore, hepatic venous outflow obstruction in BCS can lead to severe liver failure; without treatment, severe congestion and necrosis lead to fibrosis and ultimately cirrhosis.23–26 In some patients, liver function deteriorates so rapidly that they present with acute liver failure.

Due to the various clinical manifestations of BCS, an early histological evaluation to determine severity of the hepatocellular damage is usually recommended, but its role in management and prediction of outcome remains controversial.27 Histologically, BCS can present with centrilobular congestion, centrilobular necrosis, lobular inflammation, portal inflammation, pericentral fibrosis, periportal fibrosis and/or cirrhosis in the most severe cases. Our patient’s liver biopsy revealed severe perivenular sinusoidal dilation with areas of confluent hepatocyte dropout, bands of hepatocyte atrophy and centrilobular fibrosis, consistent with chronic outflow obstruction/BCS (figure 4).

One study proposed a histology-based algorithm for the treatment of BCS, suggesting that patients with BCS should be treated solely with oral anticoagulants when the biopsy reveals only central lobular venous congestion with sinusoidal dilatation.28 In cases where pericentral necrosis is present, a decompressive shunt procedure (like transjugular intrahepatic portosystemic shunt) is recommended, while liver transplantation is recommended in presence of extensive fibrosis. Individuals with IBD after an initial episode of venous thromboembolic events are at increased risk of developing another episode after discontinuation of anticoagulation therapy.7

Our patient has been kept on anticoagulation therapy and no further episodes of thrombosis have occurred. BCS is a rare complication of CD and when left untreated can cause significant liver damage and can lead to death. This case recapitulates the need for a high level of suspicion and increased awareness of the venous thromboembolic risks associated with CD. Radiological imaging coupled with histological diagnosis plays an important role in early detection and assessment of the extent of disease in BCS. Appropriate intervention to mitigate hepatic congestion is essential to restore hepatic function and to alleviate portal hypertension.

REFERENCES
1. Danwil Murad S, Valla DC, De Groen PC, et al. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. Hepatology2004;39:500–8.
2. Maccini DM, Berg JC, Bell GA, Budd-Chiari syndrome and Crohn’s disease. An unreported association. Dig Dis Sci 1989;34:1933–6.
3. Witteman BJ, Wetterman IT, Griffiesen G, et al. [Intestinal obstruction caused by non-absorbable tablets and Budd-Chiari syndrome in a patient with Crohn’s disease]. Ned Tijdschr Geneeskd 1991;135:766–9.
4. Schäfer C, Zundler J, Bode JC. Thrombolytic therapy in patients with portal vein thrombosis: case report and review of the literature. Eur J Gastroenterol Hepatol2000;12:1141–5.
5. McCabe JM, Mahadevan U, Vidyanthi A. An obscure harbinger. Difficult diagnosis of Crohn’s Disease. Am J Med 2009;122:516–8.
6. Valdés Mars M, Martínez Pascual C, Egea Valenzuela J, et al. Bilateral pulmonary thromboembolism and Budd-Chiari syndrome in a patient with Crohn’s disease on oral contraceptives. Rev Esp Enferm Dig 2009;101:645–52.
7. Brinar M, Hrstic I, Cukovic-Cavka S, et al. Chronic Budd-Chiari syndrome as a rare complication of Crohn’s disease: a case report. Eur J Gastroenterol Hepatol2010;22:761–4.
8. Solem CA, Lofthus EV, Tremaine WJ, et al. Venous thrombosis in inflammatory bowel disease. Am J Gastroenterol2004;99:97–101.
9. Zitomersky NL, Verhave M, Tencer CC. Thrombosis and inflammatory bowel disease: a call for improved awareness and prevention. Inflamm Bowel Dis 2011;17:458–70.
10. Novacek G, Weltermann A, Sobala A, et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. Gastroenterology2010;139:779–87.
11. Wakefield AJ, Sawyer AM, Dillon AP, et al. Pathogenesis of Crohn’s disease: multifocal gastrointestinal infarction. Lancet1989;2:1057–62.
12. Webberley MH, Hart MT, Melkian V. Thromboembolism in inflammatory bowel disease: role of platelets. Gut1985;24:247–51.
13. Oldenburg B, Van Tuijl BA, van der Griend R, et al. Risk factors for thromboembolic complications in inflammatory bowel disease: the role of hyperhomocysteinaemia. Dig Dis Sci2005;50:235–40.
Unusual association of diseases/symptoms

14 Chiarantini E, Valanzano R, Liotta AA, et al. Hemostatic abnormalities in inflammatory bowel disease. Thromb Res 1996;82:137–46.
15 Gris JC, Schved JF, Raffanel C, et al. Impaired fibrinolytic capacity in patients with inflammatory bowel disease. Thromb Haemost 1990;63:472–5.
16 Koutroubakis IE. Role of thrombotic vascular risk factors in inflammatory bowel disease. Dig Dis 2000;18:161–7.
17 Koutroubakis IE, Petinaki E, Aranghodopoulou E, et al. Anti-cardiolipin and anti-beta2-glycoprotein I antibodies in patients with inflammatory bowel disease. Dig Dis Sci 1998;43:2507–12.
18 Saibeni S, Vecchi M, Valsecchi C, et al. Reduced free protein S levels in patients with inflammatory bowel disease: prevalence, clinical relevance, and role of anti-protein S antibodies. Dig Dis Sci 2001;46:637–43.
19 Saibeni S, Spina L, Vecchi M. Exploring the relationships between inflammatory response and coagulation cascade in inflammatory bowel disease. Eur Rev Med Pharmacol Sci 2004;8:205–8.
20 Koutroubakis IE, Sfiridaki A, Tsiliolakidou G, et al. Genetic risk factors in patients with inflammatory bowel disease and vascular complications: case-control study. Inflamm Bowel Dis 2007;13:410–5.
21 Valla DC. Budd-Chiari syndrome and veno-occlusive disease/sinusoidal obstruction syndrome. Gut 2008;57:1469–78.
22 Ha C, Magowan S, Accott NA, et al. Risk of arterial thrombotic events in inflammatory bowel disease. Am J Gastroenterol 2009;104:1445–51.
23 Shetty S, Ghosh K. Thrombophilic dimension of Budd chiari syndrome and portal venous thrombosis—a concise review. Thromb Res 2011;127:505–12.
24 Koutroumpakis EL, Tsiliolakidou G, Koutroubakis IE. Risk of venous thromboembolism in patients with inflammatory bowel disease. Semin Thromb Hemost 2013;39:461–8.
25 Valla D, Benhamou JP. Obstruction of the hepatic veins or suprahepatic inferior vena cava. Dig Dis 1996:14:99–118.
26 Dilawari JB, Bambery P, Chawla Y, et al. Hepatic outflow obstruction (Budd-Chiari syndrome). Experience with 177 patients and a review of the literature. Medicine 1994;73:21–36.
27 Henderson JM, Warren WD, Millikan WJ, et al. Surgical options, hematologic evaluation, and pathologic changes in Budd-Chiari syndrome. Am J Surg 1990;159:41–50.
28 Millikan WJ, Henderson JM, Sewell CW, et al. Approach to the spectrum of Budd-Chiari syndrome: which patients require portal decompression? Am J Surg 1985;149:167–76.