

Budd-Chiari syndrome in Behcet's disease: A report of two cases

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Received May 30, 2018; Accepted November 1, 2018

DOI: 10.3892/etm.2018.7130

Abstract. Budd-Chiari syndrome (BCS) is a rare but severe venous form of Behcet's disease (BD) that is caused by the obstruction of the venous outflow tract that transports blood from hepatic veins into the inferior vena cava. In countries where BD is prevalent, including the Middle East and Far East, BCS awareness is important. In the present study, two cases of BCS are presented in two male Chinese patients with BD. The clinical characteristics, treatment and outcomes were recorded and compared with previous studies, and the features of BD-BCS were summarized. The clinical characteristics of the two patients documented were similar. Each patient presented with insidious onset, abdominal symptoms and recurrent aphthous ulcers. Accurate diagnosis was delayed as other symptoms of BD were overlooked. Each patient responded well to TNF- α inhibitor treatment in combination with cyclophosphamide (CYC). One patient with good compliance was removed from CYC and corticosteroid therapy. Unfortunately, the other patient with poor compliance faced a poor outcome. It was concluded that multiple vessel lesions in ≥ 2 sites are common in vasculo-BD and that misdiagnosis may occur if other symptoms of BD are not noticed. BD-BCS is associated with a high mortality rate, but appropriate treatment may result in a favorable outcome.

Introduction

Behcet's disease (BD) is a chronic multisystem of relapsing vasculitis with an unknown etiology that is characterized by oral and genital ulceration, cutaneous lesions, ocular inflammation, arthritis and vascular manifestations (1).

The diagnosis of BD is clinical and no specific laboratory findings are included in the diagnostic criteria (1). BD associated vasculitis affects vessels of all sizes in the arterial and venous systems (2-4). Vasculitis with thrombosis

in large vessels is common, with lower extremity deep vein thrombosis being the most common form of BD vascular involvement (2-4). Budd-Chiari syndrome (BCS) is caused by the thrombotic or non-thrombotic obstruction of the venous outflow tract that transports blood from hepatic veins into the inferior vena cava (1,2). Patients with BCS are at a high risk of portal hypertension and liver failure, but thrombosis is the primary cause of BCS (5). It has been reported that ~5% of patients with BCS in western countries, 9% in Turkey and 13% in Egypt may be attributed to BD (6-9). However, misdiagnosis is a common occurrence in cases of BD associated BCS (BD-BCS) (8,9). Certain patients exhibit no overt symptoms and others experience abdominal pain, jaundice, nausea, enlarged liver/spleen and ascites (8,9). Inappropriate or delayed treatment may therefore occur if other symptoms of BD are unnoticed. Although BD-BCS is more common in the Middle and Far East, it has been rarely observed in China. Herein, two cases of BD-BCS are reported and a literature review is presented. The clinical characteristics, treatments and outcomes of the patients admitted to The First Affiliated Hospital of Sun Yat-sen University between 2004 and 2016 were assessed.

Case report

Ethics statement. The present study was performed in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University [Guangzhou, China; Project identification code: (1481) 541729]. Informed consent was obtained from each patient for publication.

Case 1. A 49-year-old Chinese man was admitted on January 2010 to the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) with a choking sensation in the chest, and abdominal distention with epigastric pain of an unknown origin. The pain was gradually worsening and was not accompanied by constipation, diarrhea or urinary symptoms. A review of the patient's medical history revealed that they had experienced oral and genital ulcers for >10 years. Oral ulcers occurred >10 times per year and genital ulcers were exhibited 5-6 times per year, all in the same location. The patient also reported episodes of uveitis. Physical examination identified oral ulcers, bilaterally decreased pulmonary breathing sounds, hepatomegaly without pressing pain, jugular varicosity and varicose veins over the abdominal wall.

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Key words: Behcet's disease, Budd-Chiari syndrome, treatment

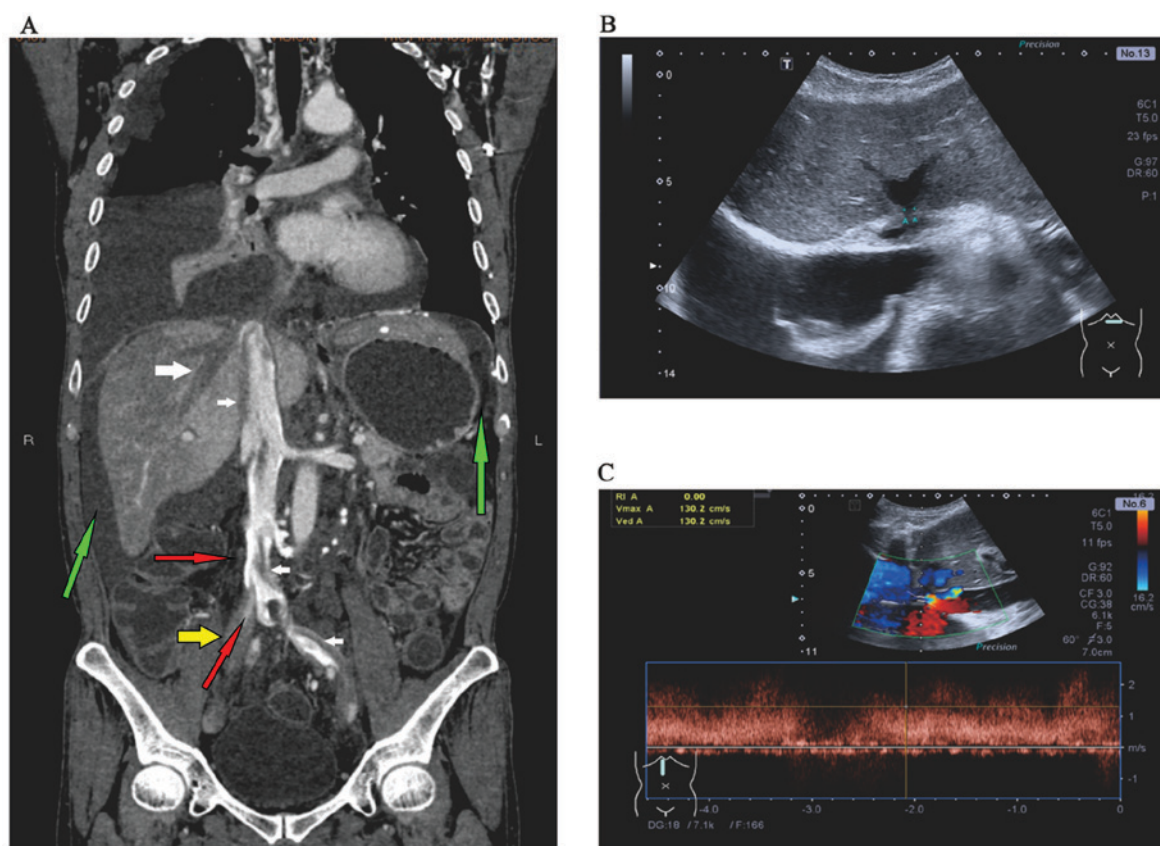


Figure 1. Case 1. Abdominal computed tomography in case 1 revealed: (A) A thrombus in the hepatic vein (large white arrow), a mural thrombus in the inferior vena cava (small white arrows) and a thrombus in the right common iliac vein (yellow arrow) were observed. There was also evidence of free fluid (green arrows) and collaterals (red arrows). (B) Ultrasound revealed stenosis of the second hepatic hilum (small blue cross, marked with an 'A' beneath). (C) Color Doppler sonography revealed stenosis of the inferior vena cava and faster blood flow at the site of stenosis.

The laboratory results were as follows: White blood cell count, $11.14 \times 10^9/l$ (normal range, $4-10 \times 10^9/l$; assessed using the Mindray BC-6900 kit; Mindray, Shenzhen, China); C-reactive protein (CRP), 49.9 mg/l (normal range, 0.00-10.00 mg/l; assessed using the CRP-M100 kit; Mindray); erythrocyte sedimentation rate (ESR), 38 mm/h (normal range for males, 0-15 mm/h); Total bilirubin (TBIL), $22.7 \mu\text{mol/l}$ (normal range, $3.0-22.0 \mu\text{mol/l}$); Glutamic pyruvic transaminase (ALT), 137 U/l (normal range, 0-40 U/l); Glutamic oxaloacetic transaminase (AST), 208 U/l (normal range, 29-35 U/l); Serum albumin (ALB), 22.3 g/l (normal range, 35.0-50.0 g/l). ESR, TBIL, ALT, AST and ALB were all assessed using the Beckman Coulter power processor that contained all the required reagents (Beckman Coulter, Inc., Brea, CA, USA). The patient was tested negative for the anti-nuclear antibody (ANA), anticytoplasmic antibody (ANCA) and anti-cardiolipin antibody (ANA, ANCA and anti-cardiolipin antibody were assessed using Oumeng Euroline Plus (Laboratory Overall Solution, Beijing, China; with its self-contained reagents). Abdominal computed tomography (CT) presented thrombus in the hepatic vein (Fig. 1A; large white arrow), mural thrombus in the inferior vena cava (Fig. 1A; small white arrows) and thrombus in the right common iliac vein (Fig. 1A; yellow arrow). There was also evidence of free fluid (Fig. 1A; green arrows) and collaterals (Fig. 1A; red arrows). An ultrasound revealed stenosis of the second hepatic hilum (Fig. 1B) and evidence of pleural effusion and ascites. Color Doppler

sonography revealed stenosis of the inferior vena cava and increased blood flow at the site of stenosis (Fig. 1C). Together, these results lead to the diagnosis of BCS.

Following the diagnosis of BCS due to BD, the patient received IV methylprednisolone (60 mg) once a day for 2 weeks and pulse intravenous cyclophosphamide (CYC; 600 mg every 2 weeks). However, pleural fluid and abdominal distention persisted. The patient was then administered infliximab (5 mg/kg) in addition to ongoing IV CYC and methylprednisolone treatment. The case study responded well to this treatment following 2 doses of infliximab (repeated after 2 weeks) at which point the symptoms resolved, and CRP fell to a normal level. Methylprednisolone was then administered orally and tapered to 4-8 mg per week.

However, following discharge after ~1 month of hospital admission, the patient terminated infliximab treatment due to financial issues. He was admitted to two other hospitals multiple times every 2-3 months and was administered aperiodic anticoagulants including warfarin (the specific dose or administration frequency could not be obtained). During IV CYC treatment, the patient complained of increasing abdominal distention and abdominal pain, but refused a CT scan. A year following the initial diagnosis, he was readmitted for hemoptysis and severe abdominal distention. On arrival, he was confused and oxygen saturation was 72% at 10 l/min oxygen (normal values, >90%). The doctors suggested intensive care but the family refused and left the hospital without further notification.

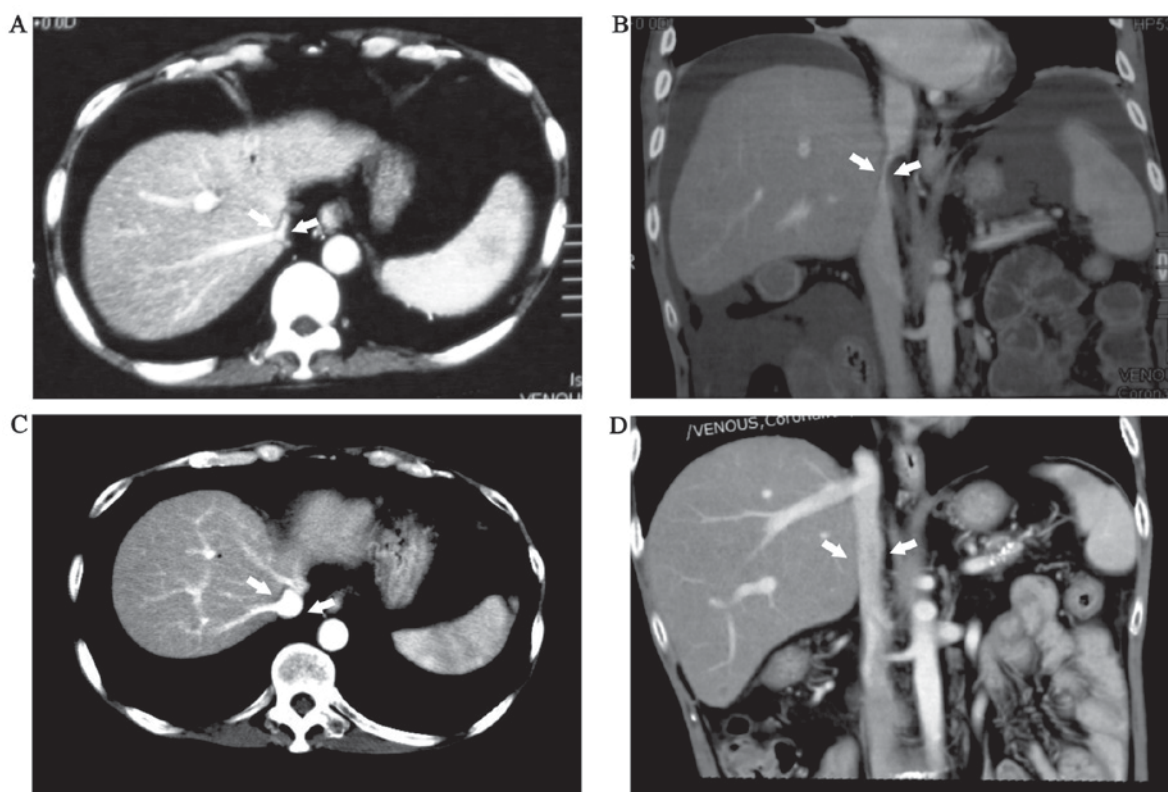


Figure 2. Case 2. Abdominal computed tomography in case 2 revealed in (A) cross plane and (B) coronal plane a narrow inferior vena cava prior to treatment (white arrows). Recovery of the inferior vena cava following infliximab treatment (5 mg/kg, 2 weeks) observed in (C) cross plane and (D) coronal plane (white arrows).

Case 2. A 43-year-old Chinese man was admitted in September 2012 with fatigue, dyspnea following exercise, abdominal distension and swelling of the legs and scrotum. In the previous 2 years, the patient had experienced recurrent abdominal distension and swelling of the legs. He had no history of drug use or other diseases. Moderate alcoholism was reported, but no smoking or family history of liver disease or thrombosis was indicated. The patient had been diagnosed with liver cirrhosis in other hospitals prior to presentation to The First Affiliated Hospital of Sun Yat-sen University, (Guangzhou, China).

Physical examination revealed fever, tachycardia, oral ulceration, swelling of the scrotum, pitting edema of leg skin, acneiform eruptions on the legs and an increasing abdominal volume. Laboratory tests are as follows: White blood cell count, $10.99 \times 10^9/l$ (normal range, $4-10 \times 10^9/l$; assessed with Mindray BC-6900, Mindray, Shenzhen, China); CRP, 9.35 mg/l (normal range, 0.00-3.00 mg/l; assessed with Mindray CRP-M100, Shenzhen, China); ESR, 38 mm/h (normal male range, 0-15 mm/h); TBIL, $21.4 \mu\text{mol/l}$ (normal range, $3.0-22.0 \mu\text{mol/l}$); ALT, 60 U/l (normal range, 0-40 U/l); AST, 134 U/l (normal range, 29-35 U/l); ALB, 24.7 g/l (normal range, 35.0-50.0 g/l). ESR, TBIL, ALT, AST and ALB were all assessed using the Beckman Coulter power processor that contained all the required reagents (Beckman Coulter, Inc.). The patient tested negative for ANA, ANCA and anti-cardiolipin antibody (assessed using the Oumeng Euroline Plus kit, Beijing, China). An abdominal CT scan revealed a narrow inferior vena cava (Fig. 2A and B).

The patient was treated with anticoagulants and responded poorly. Following a consultation with a rheumatologist and a subsequent diagnosis of BD with BCS, the patient was administered oral prednisone (30 mg/day), thalidomide (50 mg/day) and pulse intravenous CYC (500 mg every 2 weeks). The symptoms resolved following 3 weeks of treatment. The patient was subsequently discharged from the hospital and continued CYC treatment for a further 6 doses (over 12 weeks). However, the patient returned 3 months later with recurrence of ascites and swelling of the legs. He received prednisone and CYC as previously, but little improvement was observed. He was then administered IV infliximab (5 mg/kg; administered at week 0, week 2, weeks 6 and then every 8 weeks) and oral methotrexate (MTX; 15 mg weekly). The patient responded well to infliximab and symptoms resolved 10 days following 2 weeks of one repeated treatment. Abdominal CT re-examination revealed that the inferior vena cava diameter was within the normal range, which confirmed the efficacy of the treatment (Fig. 2C and D). The patient was discharged and remained on the same dosage of infliximab therapy for 6 weeks, then treatment with infliximab (5 mg/kg) every 8 weeks. Following 20 months of infliximab therapy, an attack of pneumococcal pneumonia occurred on a very small steroid dose (prednisone, 5 mg/day). Infliximab and immunosuppressant therapy was stopped and the patient was treated with cefuroxime (500 mg, twice a day for 7 days). Following resolution of the infection, the patient was discharged and MTX (10-15 mg per week) was administered for 1.5 years. Corticosteroid treatment was gradually stopped, and no recurrences of BCS symptoms

were observed up to the time of last review, which occurred 38 months following discharge.

Discussion

Vascular BD can lead to thromboses, occlusions and aneurysms, and patients are at risk of developing vessel-associated complications, resulting in a poor prognosis (10). Among all vascular involvements, lower extremity deep vein and large artery lesions are the most common (11).

Occlusion of the major hepatic veins, the adjacent inferior vena cava, or both, is termed BCS and is rarely seen in BD. It has been reported that BD-BCS accounts for 3% BCS diagnoses (12,13) and BCS is estimated to occur in 1-3% patients with BD (14). BCS can be asymptomatic for a long duration and a small proportion of cases present as fulminant hepatic failure (14). The condition of the patient depends on the rate of hepatic vein blockage and the compensatory collateral circulation (15,16). In countries where BD is prevalent, awareness of BCS is important (6). As a serious complication of BD, BD-BCS is associated with a high mortality rate (12); however, efficient medical intervention may lead to favorable outcomes. Early diagnosis is therefore important for patients with BCS to receive prompt and specific treatment (12). Furthermore, misdiagnosis may occur if the patient is not diagnosed with BD prior to BCS (8,9). Case 2 initially presented with symptoms of liver cirrhosis and was given non-specific treatment, but was diagnosed with BD 6 months later at The First Affiliated Hospital of Sun Yat-sen University. It is therefore important that rheumatologists are included at consultations for these patients. The case also revealed that corticosteroids and CYC treatment induced the first observed remission.

Treatment choices for BD-BCS are not standardized due to the lack of high quality randomized controlled trials; however, glucocorticoids, CYC, azathioprine and thalidomide are the most advocated therapies (17). Immunosuppressive agents have also been associated with favorable outcomes in numerous cases, meaning that surgical/endovascular intervention may be avoided (17). However, anticoagulation alone or in combination with surgery has not been demonstrated to be as effective as immunosuppressive agents (9). The use of anticoagulants therefore remains controversial. A previous study has demonstrated that patients who received only anticoagulation therapy had favorable outcomes (9). However, the 2008 Eular recommendation discouraged the use of anticoagulants, as they were associated with a higher risk of aneurysm rupture and bleeding (18).

The present study included two cases in which initial CYC treatment induced remission, but this was not sustained. Case 1 was unique as hemoptysis occurred during CYC treatment, which was indicative of pulmonary vascular involvement. Multiple vessel lesions and associated complications in ≥ 2 sites are common in BD (19). However, BCS and pulmonary vascular involvement occurring at the same time has not been frequently reported (19). It appeared that CYC treatment was not sufficient in case 1; however, this patient was occasionally administered anticoagulants, which may explain the observed pulmonary bleeding. An inadequate response to initial conventional immunosuppressive treatment may occur in certain patients. Tumor necrosis factor- α (TNF- α) inhibitors have been reported to be a successful alternative in CYC

refractory vasculo-BD cases (20-24). The patients described in the present study were administered add-on infliximab, either following failure of conventional therapy or relapse, and fast responses were observed. Case 2 was able to terminate their use of corticosteroids, infliximab and CYC, and a sustained remission was exhibited whilst taking MTX. Case 1 responded quickly to infliximab; however, the patient was prevented from completing therapy. TNF- α inhibitors were useful in reduced and sustained remission in the presented cases. TNF- α blockers have been used to treat various manifestations of BD (25). Previous studies have demonstrated that successful infliximab and adalimumab therapy has been achieved in vasculo-BD, uveoretinitis, entero-BD, neuro-BD and BD arthritis (25,26). TNF- α is considered a key element in the inflammatory pathway of BD. Previous studies have identified that TNF- α expression produced by $\gamma\delta$ T cells is increased in the peripheral blood of patients with active BD and TNF- α mRNA expression was revealed to decrease following TNF- α blocker treatment (27,28). Overall, the present study indicates that TNF- α targeted treatment in BD may be effective. With the advantage of producing a fast response, TNF- α blockers are relatively safe and highly tolerable compared with CYC (26). However, whether TNF- α blockers should be included in the first line treatment of BD-BCS is yet to be determined.

In summary, BCS is a rare but potentially threatening complication of BD and multiple vessel lesions in ≥ 2 sites are common. Misdiagnosis may occur if other symptoms of BD are unnoticed. Therefore, the early diagnosis and appropriate treatment of BD may lead to favorable outcomes. Furthermore, CYC and corticosteroids are effective in the majority of cases.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 81102270) and the Guangdong Natural Science Foundation (grant nos. 2014A030313053 and 2016A030313217).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, but no information infringing on the privacy of the participants will be given.

Authors' contributions

FL and JZ conceived and designed the current study. YW, HX and FL collected the data. JZ, YW, YL and HZ analyzed the data, JZ and FL wrote the manuscript. All authors read and approved the final manuscript

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by

the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [Guangzhou, China; Project identification code, (1481) 541729].

Patient consent for publication

All patients provided their consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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