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Budd–Chiari syndrome associated to Behcet disease

An observational retrospective multicenter study in Morocco

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Abstract

Budd–Chiari syndrome (BCS) is considered a rare but serious complication of Behçet's disease (BD). This study was performed to define the prevalence, clinical and biological features, treatment, and clinical course of BSC associated with BD in a Moroccan population. We retrospectively analyzed the medical records of 1578 patients fulfilling the international diagnostic criteria for BD, including those with BSC. Eighteen male and 3 female patients, with a mean age of 36 ± 8.6 years. The inferior vena cava was involved in 81% (n = 17) of cases. All forms of BCS were noted: the chronic form in 52.4% (n = 11), the subacute form in 38% (n = 8), and the fulminant form (2 cases). Ascites was the main clinical sign and was present in 62% of patients (n = 13). Other venous thromboses (superior vena cava and lower limbs) were associated with BSC in 52.4% of patients (n = 11). Arterial involvement was noted in 28.6% (n = 6). Cardiac manifestations were present in 19% (n = 4) of the patients. All the patients received anticoagulants associated with corticosteroids. Immunosuppressants were used in 95% (n = 20). One patient received infliximab. Severe complications were noted in 38% (n = 8) of patients (digestive bleeding, confusion, infections and liver failure). Four patients have died during the study period. BCS in patients with BD is not uncommon and can be life threatening. It is frequently associated with other vascular manifestations that can be difficult to treat, particularly in the presence of pulmonary artery aneurysms. Prognosis improved with the use of immunosuppressants. Biologics can be promising in the early stages.

Abbreviations: BCS = Budd–Chiari syndrome, BD = Behçet's disease.

Keywords: anticoagulation, anti-TNFα,·Budd–Chiari syndrome,·Behcet disease,·immunosuppressants

1. Introduction

Budd–Chiari syndrome (BCS) is defined, according to the European Group for the Study of Hepatic Vascular Diseases, as hepatic venous outflow obstruction at any level from the small hepatic veins to the junction of the inferior vena cava and the right atrium, regardless of the cause of the obstruction.[1] In Behcet disease (BD), it is considered as a rare complication that can be life-threatening.[2] Mortality can be caused by liver failure, bleeding of varicose veins, or refractory ascites.[3] A few series and case reports have described this condition in BD, especially in a population located in northern Africa. This study was performed to define the prevalence, clinical features, laboratory findings, treatment, and clinical course of BCS associated with BD in a Moroccan cohort.

2. Patients and Methods

From January 1989 to August 2021, out of a total of 1578 patients with BD fulfilling the international diagnostic criteria for Behcet's disease,[4] we selected those who had BCS. We retrospectively analyzed the patients' medical records and determined their demographic, clinical, and biological characteristics and outcomes. The study was multicenter and was conducted in 2 major university hospitals in Casablanca (Morocco), which are the reference centers for BD in Morocco. The diagnosis of BCS was confirmed by Doppler ultrasonography and/or computed tomography. BCS was defined as any thrombotic occlusion localized in the hepatic veins or at the hepatic or suprahepatic segments of the inferior vena cava. We also screened the patients for other conditions that may

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The authors have no ethical statement and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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be responsible for hypercoagulability and/or liver impairment (levels of protein C, protein S, antithrombin III, antiphospholipid antibodies, antinuclear antibodies, Janus Kinase 2 mutations/viral hepatitis B and C, human immunodeficiency virus, and neoplastic diseases). Some prothrombotic factors were also noted (pregnancy, contraceptive pills, obesity, and smoking).

We obtained the patients informed consent before the submission of the manuscript and our ethical board have approved our study.

3. Results

Twenty-one patients of the 1578 patients with BD were diagnosed with BCS, giving a prevalence of 1.3 in 100 patients. Eighteen male and 3 female patients, with a mean age of 36 ± 8.6years. Budd–Chiari syndrome was indicative of the disease in 8 patients (38%). The mean interval between the onset of BD and the occurrence of BCS was 4 ± 2.9 years (Table 1).

The inferior vena cava was involved in 81% (n = 17) of cases, and hepatic vein thrombosis was found in 24% (n = 5) (Fig. 1). All forms of Budd–Chiari were noted: chronic form in (n = 11) 52.4%, subacute form in 38% (n = 8), and fulminant form in 2 cases. Ascites was the main clinical sign (Fig. 2) present in 62% (n = 13) of the cases, while collateral venous circulation was present in 57% (n = 12) (Fig. 3), abdominal pain in 52.3% (n = 11), hepatomegaly in 19% (n = 4),and jaundice in 14.3% (n = 3). Two patients presented with digestive bleeding and impaired consciousness (Table 1). In 1 case, the patient had a history of deep venous thrombosis affecting both legs. The patient was clinically asymptomatic, with abnormal liver function tests as a unique sign (Table 2).

Other venous thromboses (superior vena cava in 14.3% (n = 3) and lower limbs in 38% (n = 8)) were associated with BCS in 52.4% (n = 11). We noted that 19% (n = 4) of patients had a history of venous thrombosis. No family history of venous

Table 1

Demographic and clinical features of Behçet's disease with Budd–Chiari syndrome.

Values	(n = 21); n (%)
Age, (mean ± SD) (years)	36 ± 8.6
Gender (male)	18 (86)
Age at diagnosis of BD, med (range) (years)	26 (15–55) 28 (16–54)
Age at diagnosis of BCS, med (range) (years)	29.6 (15–55)
Duration between first symptom of BD and diagnosis of BCS (mean ± SD) (years)	4 ± 2.9
Current smoker	8 (38)
BD in the family	1 (4.8)
Clinical findings	
Oral ulcer	21 (100)
Genital ulcer	17 (81)
Papulopustular lesion	6 (28.6)
Erythema nodosum	3 (14.3)
Pathergy test positive	6 (28.6)
Ocular involvement	5 (24)
Joint involvement	10 (47.6)
CNS involvement	2 (9.5)
Vascular involvement	17 (81)
Child–Pugh score	
Child–Pugh A	10 (47.6)
Child–Pugh B	6 (28.6)
Child–Pugh C	3 (14.3)
BSC location	
The inferior vena cava thrombosis	17 (81)
Hepatic vein thrombosis	5 (24)
Pulmonary artery aneurysm	1 (4.8)
Cardiac thrombus	3 (14.3)
Coronary artery aneurysm	1 (4.8)

BD = Behcet's disease, BCS = Budd–Chiari syndrome, CNS = central nervous system.

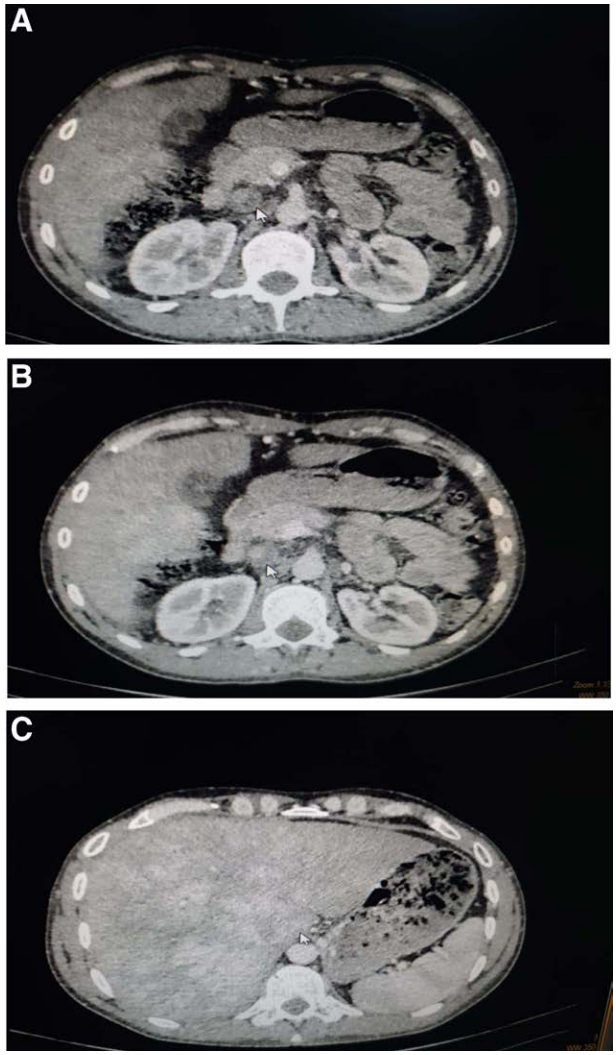

Figure 1. (A and B) Lack of opacification of the inferior vena cava and hepatic veins, indicating Budd–Chiari syndrome. (C) Liver enlarged in size, heterogeneous density, without nodular lesion, enhancing heterogeneously indicating a perfusion disorder.

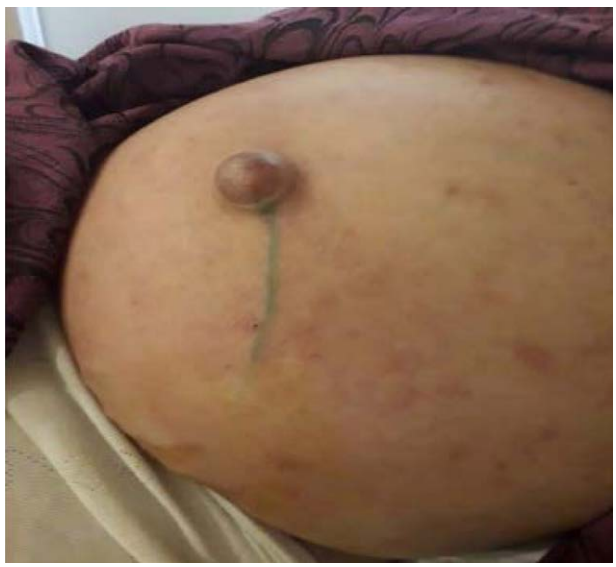

Figure 2. An enlarged abdomen in a female patient with Budd–Chiari associated to Behcet disease indicating ascites.

thrombosis was noted. Arterial involvement was noted in 28.6% (n = 6) of cases (pulmonary embolism in 24% [n = 5] and pulmonary artery aneurysm in 1 case). Cardiac manifestations were also present in 19% (n = 4) (3 intracardiac thrombosis and 1 coronary aneurysm [Fig. 4]). Oral ulcers were noted in 100% (n = 21) of the patients, genital ulcers in 81% (n = 17), ocular involvement in 24% (n = 5), and central nervous system involvement in 9.5% (n = 2) (Table 1). Bladder vasculitis was associated with BCS in 1 patient. All female patients were on contraceptive pills at the time of BCS diagnosis. Smoking habits were present in 38% (n = 8) of the patients (Table 1). No patient was obese.

Liver function tests were abnormal in 52.3% (n = 11) of patients, with liver failure in 33% (n = 7), cholestasis in 19% (n = 4), and cytolysis in 33% (n = 7). The mean serum alanine aminotransferase level of alanine aminotransferase was 114 ± 52.6 IU/L. The mean alkaline phosphatase and conjugated bilirubin levels were 82 ± 42.3 mg/L and 13 ± 5.6 mg/L, respectively. The mean γ-glutamyl transferase level was 83 ± 62.2 mg/L. The mean prothrombin ratio and serum albumin levels were 65% (range 23–82) and 35.7 ± 26.3 g/L, respectively (Table 3). Creatinine levels were elevated in 9.5% (n = 2) of patients. Inflammatory parameters were elevated in 28.6% of patients (n = 6). According to the Child-Pugh score, 47.6% (n = 10) of our patients were classified as Class A, 28.6% (n = 6) as Class B, and 14.3% (n = 3) as Class C (Table 1). Two patients tested positive for anti-phospholipid antibodies. Antinuclear antibodies were negative in all patients tested. Eleven patients were screened for Janus Kinase 2 mutations and were found to be negative. Plasma levels of proteins C and S, as well as antithrombin III, were all within normal ranges. Hepatitis B and C and human immunodeficiency virus testing results were negative in all patients. Neoplastic investigations were negative for all patients. Gastroscopy was performed in 52.3% (n = 11) of patients and esophageal varices in 14.3% (n = 3). No liver biopsies were performed.

All patients received anticoagulation therapy, which was delayed in 1 case after regression of the pulmonary aneurysm, associated with high-dose corticotherapy in all cases. Eight patients initially received methylprednisolone pulses; the usual daily dose of oral corticosteroids was 30 to 60 mg administered as a single dose for 4 weeks. Cyclophosphamide or azathioprine were used in 95% (n = 20) of cases (cyclophosphamide in 76.2% [n = 16], azathioprine in 62% [n = 13]). One patient did not receive immunosuppressive therapy and presented with superior vena cava thrombosis 16 years later. One patient received infliximab for a relapse. Diuretics were required in 43% (n = 9) of patients. Propranolol was used in 2 cases to prevent digestive bleeding. No surgical interventions were performed.

Table 2

Clinical characteristics of Budd–Chiari syndrome patients with Behçet's disease.

Values	(n = 21); *n*(%)
Abdominal pain	11 (52.3)
Digestive bleeding	2 (4.2)
Ascites	13 (62)
Collateral venous circulation	12 (57)
Encephalopathy	2 (4.2)
Hepatomegaly	4 (19)
Jaundice	3 (14.3)

Ascites improved in 71.4% (n = 15) of the cases and was refractory in 2 patients. Severe complications were noted in 38% (n = 8) of patients, digestive bleeding in 14.3% (n = 3), encephalopathy in 9.5% (n = 2), infections in 14.3% (n = 3) (a case of pulmonary tuberculosis, a case of bacterial pulmonary infection, and another case of bacterial cutaneous infection), and liver failure in 23.8% (n = 5). No cases of hepatocellular carcinoma were diagnosed.

The mean follow-up duration was 84 months ± 76.3. Death occurred in 19% of patients (n = 4). The mean time between BCS diagnosis and death was 12 months ± 10.3. The main cause of mortality was liver failure in 3 patients with hepatic vein thrombosis, followed by infection in 1 case with inferior vena cava thrombosis.

4. Discussion

In comparison to deep vein thrombosis of the lower extremities, BCS is less common in vascular Behçet.[5] BD is considered a common cause of BCS, especially in cases where BD is endemic.[6,7]

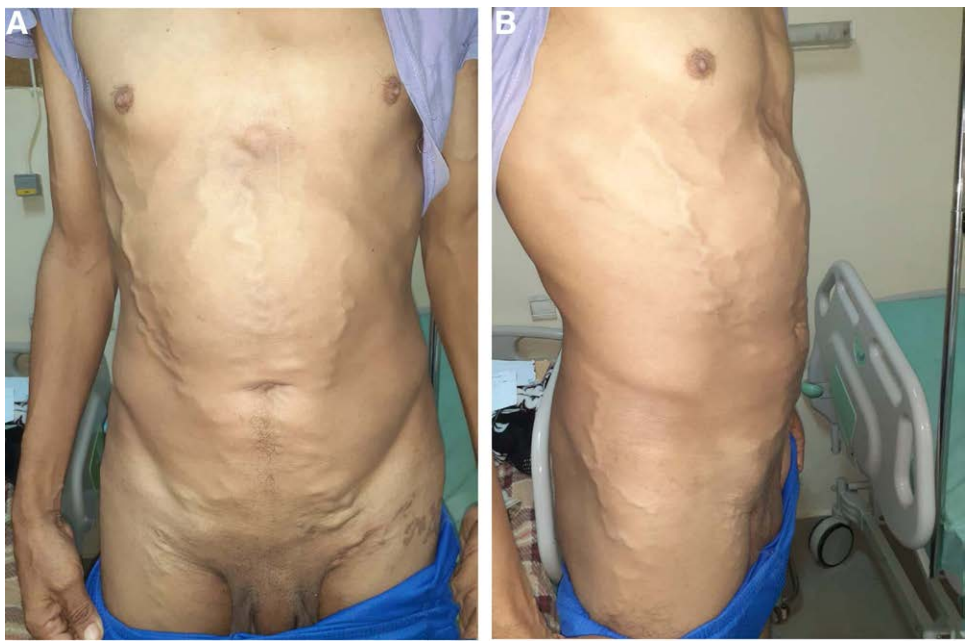

Figure 3. Thoracic and abdominal collateral venous circulation in a male patient with Budd–Chiari associated to Behcet disease with superior and inferior vena cava thrombosis.

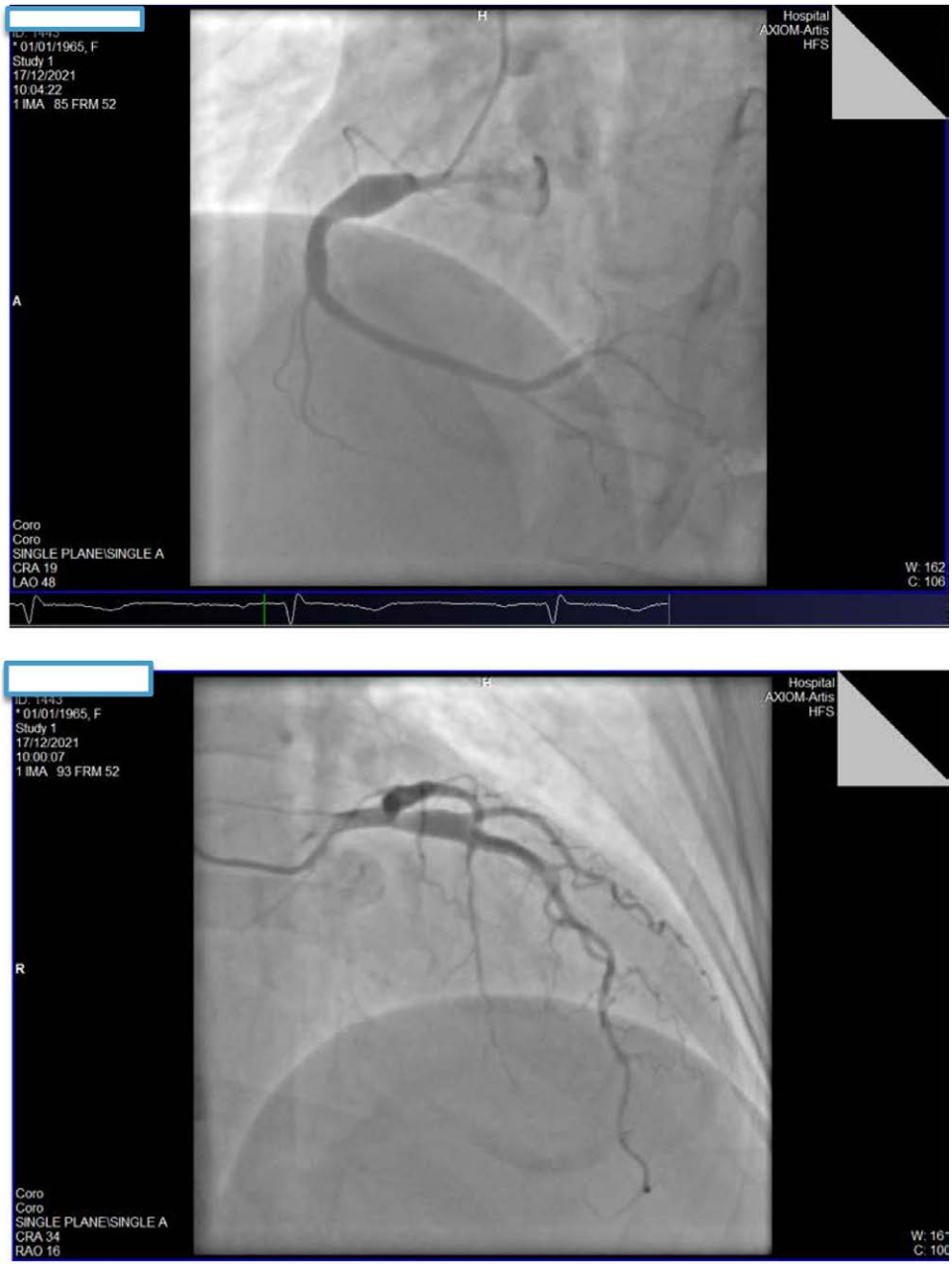

Figure 4. Coronary aneurysms in a female patient with Budd–Chiari associated to Behcet disease.

Table 3

Laboratory characteristics of Budd–Chiari syndrome patients with Behçet's disease.

Values (mean ± SD)	
ALT (UI/L)	114 ± 52.6
AST (UI/L)	82 ± 12.3
ALB(g/L) (UI/L) UI/L)	35.7 ± 26.3
Alkaline phosphatase (mg/L)	82 ± 42.3
γ-glutamyl transferase (mg/L)	83 ± 62.2
BIL D (mg/L)	13 ± 5.6
PT (range)	65% (23–82)
ESR (range)	23 (13–35)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALB = albumin, BIL D = bilirubin direct, ESR = erythrocyte sedimentation rate, PT = prothrombin time.

The frequency of BCS in patients with BD ranges from 0.3% to 26%.[8,9] This variation is probably due to a referral bias, considering the contribution of gastroenterology units in some studies. In our study, the prevalence was 1.3%, and we think that this number is just the tip of the iceberg, and that there are some cases of BCS in our series that are not diagnosed, especially asymptomatic ones. We also believe that we should always search for BD in patients with BCS, especially in young men. It is well established that vascular involvement is more common in young males,[5–10] as the majority of our patients.

The inferior vena cava was involved in 80% of the cases; this is the main characteristic of BCS in BD, which has also been reported in other studies,[5–11] and is uncommon in BCS due to other causes.[13,14]

In this study, hepatic vein thrombosis was found in 5 patients, 3 of them (from 5) died of liver failure. Hepatic vein thrombosis

in patients with BD may have a poor prognosis.[15] We also noted that the portal vein was not involved in our series, a feature that was also reported in a large survey,[11] we did not find an explanation for this observation at the time of this study.

The clinical features of BCS in our patients were similar to those described previously for other causes, with a prevalence of ascites, abdominal pain, and collateral circulation.[14] We have observed 2 cases of big interest: 1 patient, with BD and a history of major vessel involvement, was totally asymptomatic and was screened for BCS when noticing a chronic liver enzyme elevation in his blood tests during follow-up; it is interesting to note that such patients seem to have a better prognosis, due to the spontaneous development of large intrahepatic and portosystemic collaterals,[7–16] and it also tells us that some patients may develop silent BCS and may remain undiagnosed during numerous years and will not benefit from an early treatment, some authors tend to suggest a systematic search for BCS, especially among all BS patients with major vascular disease[11]; the second observation concerned cases where the diagnosis of BD had not been made yet when BCS occurred, so it is important to keep in mind that BCS may be the presenting manifestation of BD, especially in endemic areas of BS.[15]

The relevant features in BD patients with BCS is the presence of symptoms related to thrombosis in other territories, with both venous and arterial involvement; our patients presented in addition to their BCS, with pulmonary artery and coronary aneurisms, intracardiac thrombosis, superior vena cava and lower limbs thrombosis. Apart from lower limb thrombosis, these are unusual vascular manifestations that should suggest a search for BD. Venous thrombosis in both legs was indicative of inferior vena cava thrombosis and by the same means of BCS in 1 case, so we found that it is an interesting fact to search for BCS in such cases, even without any liver-related symptoms.

With regard to treatment, the diagnosis of BS in a patient with BCS becomes very important because mortality is extremely high if treated with only anticoagulation without an immunosuppressive approach,[6–15] whereas BCS from other causes would be treated mainly with anticoagulants along with endovascular treatment or surgery.[17] Knowing the pathergy reaction of BS to penetrating trauma, these procedures may be risky for BS patients.[11–18] Endovascular treatment can be beneficial in difficult cases with resistance to medical treatment.[19] In our study, only 1 patient did not receive immunosuppressive treatment because he was diagnosed and treated before the 1990s, when immunosuppression was scarcely used for vascular involvement. None of the patients had undergone endovascular or surgical procedures. The mortality in our study (19%) was comparable to that observed in BCS due to other causes (20–30%),[13–20] while it was higher (47%) in a survey where 43 BD patients with BCS were mainly treated with cyclophosphamide.[11] The mortality rate in our study may be explained by the large use of immunosuppressors and the fact that most of our patients had chronic BCS and a large collateral circulation. Anti-tumor necrosis factor-α agents are increasingly used in BD, and their use in major vessel involvement, especially in BCS, is rarely reported. It was used in 1 patient in our study who relapsed under conventional immunosuppressive therapy. In a recent study, they were used with efficacy in 2 cases of BCS among 18 patients with major vessel disease.[22] Seyahi. et al reported 3 patients with BD and BCS treated with infliximab. Two patients had end-stage liver disease when infliximab was initiated and died from hepatic failure, and there was a limited benefit in the third patient, who was stabilized after etanercept but had a relapse of dural sinus thrombosis.[18] A fourth patient was later reported by the same team, where infliximab was proven to be successful in controlling disease activity.[11]

Our study has some limitations as the reduced number of patients, its retrospective and observational design but it can lay grounds to longitudinal and more broad studies.

All these conclusions were based mainly on case reports and retrospective series; to minimize bias, randomized and controlled trials are strongly needed, which can be achieved by encouraging collaborative studies. In conclusion, BCS in patients with BD is not uncommon and can be life threatening. This study shows that BD should be screened in BCS patients, especially young males; with inferior vena cava thrombosis, and in the presence of thrombosis in other territories, in addition to BCS. The prognosis was improved with the use of immunosuppressive therapy in addition to anticoagulation. Invasive procedures should be rarely used. It can be difficult to treat in the presence of pulmonary artery aneurysms because of the increased risk of aneurysm rupture. Anti-tumor necrosis factor-α agents can improve refractory cases but this should be confirmed by larger studies.

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