Budd–Chiari syndrome associated with Behçet’s disease

Syndrome de Budd-Chiari au cours de la maladie de Behçet

I. Ben Ghorbel, R. Ennaifer *, M. Lamloum, M. Khanfir, M. Miled, M.H. Houman

Department of Internal Medicine, La Rabta Hospital, 1007 Jabbari Tunis, Tunisia

Available online 9 April 2008

Summary

Objectives. — Budd–Chiari syndrome is a rare and serious complication of Behçet’s disease, and is the result of occlusion of the major hepatic veins, the adjacent inferior vena cava, or both. The aim of this study was to determine the prevalence, clinical and laboratory findings, and treatment and clinical course of Budd–Chiari syndrome associated with Behçet’s disease.

Methods. — We analyzed retrospectively the charts of 220 patients fulfilling the international diagnostic criteria of Behçet’s disease. From them, we selected those with Budd–Chiari syndrome, and analyzed their epidemiological and clinical imaging features and outcomes.

Results. — Seven male patients, mean age 29 years and already diagnosed with Behçet’s disease, had Budd–Chiari syndrome. The clinical course was from subacute to chronic in all cases. Thrombosis of hepatic veins was associated with inferior vena cava thrombosis in six cases. Four patients had other venous thromboses (superior vena cava and lower limbs) and one also had pulmonary emboli. One patient was positive for anticardiolipin antibodies. All patients had anticoagulation therapy, and six had high-dose corticotherapy associated, in two cases, with monthly cyclophosphamide intravenous pulses. Clinical outcome was favourable in six cases, and one patient died of hepatic failure.

Conclusion. — The prevalence of Budd–Chiari syndrome in patients with Behçet’s disease is 3.2%, confirming that this syndrome is not uncommon in Behçet’s patients. The inferior vena cava is frequently involved in combination with hepatic veins and often associated with other venous thrombosis. The prognosis may be favorable with medical interventions, including anticoagulation, treatment of the vasculitis and the use of diuretics when required.

© 2008 Elsevier Masson SAS. All rights reserved.

* Corresponding author.
E-mail address: rym.ennaifer@yahoo.fr (R. Ennaifer).

0399-8320/ $ - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.gcb.2007.12.022
Introduction

Budd—Chiari syndrome (BCS), due to occlusion of the major hepatic veins, the adjacent inferior vena cava, or both, is a rare and serious complication of Behçet’s disease (BD) [1]. Approximately 55 cases of BCS in patients with BD have been reported in the literature [1—5]. Although the mortality rate of BD is only 2—3% [6], up to two-thirds of the patients with BD who develop BCS can die as a consequence of hepatic venous outflow obstruction [1].

The aim of this retrospective study was to determine the prevalence of BCS in patients with BD, to present the clinical and laboratory findings of this entity, and to estimate its prevalence of BCS in patients with BD, to present the clinical and laboratory findings of this entity, and to estimate its prevalence of BCS in patients with BD, and to evaluate the outcomes. The diagnosis of clinically suspected BCS was confirmed in all cases by doppler duplex ultrasonography and/or computed tomography (CT) of the abdomen. Percutaneous liver biopsy was performed in one case. Levels of protein C, protein S and antithrombin were evaluated in each case. Screening for antibodies—glycoprotein-1 and anticardiolipin antibodies was also performed in all patients. All patients were also tested for viral hepatitis B and C.

Patients and methods

From January 1987 to June 2005, out of a total of 220 patients with BD, we selected those who had BCS. All patients fulfilled the diagnostic criteria of the International Study Group of BD [7]. We retrospectively analyzed the epidemiological and clinical imaging features as well as the outcomes. The diagnosis of clinically suspected BCS was confirmed in all cases by doppler duplex ultrasonography and/or computed tomography (CT) of the abdomen. Percutaneous liver biopsy was performed in one case. Levels of protein C, protein S and antithrombin were evaluated in each case. Screening for antibodies—glycoprotein-1 and anticardiolipin antibodies was also performed in all patients. All patients were also tested for viral hepatitis B and C.

Results

Seven of the 220 patients with BD were diagnosed as having BCS, giving a frequency of 3.2%. All were men with a mean age at diagnosis of 29 years (range 25—34 years), and all had been diagnosed as having BD at the time of BCS presentation. The time interval between the onset of BD and the occurrence of BCS ranged from one to three years, with an average time of 2.2 years.

All patients were symptomatic. Hepatomegaly, collateral venous circulation and lower-limb edema were present in all patients, ascites in six cases and enlarged spleen in three cases. The BCS course ran from subacute to chronic in all cases [8]. None of the patients presented with ocular involvement at the time of diagnosis. Two had central nervous system involvement: one had hemiplegia occurring nine months before BCS; the other had dystonic movements related to a left occipital lesion on cerebral CT from three years ago. Thrombosis of hepatic veins was associated with inferior vena cava thrombosis in six cases.

Apart from BCS, four patients had other venous thromboses: in the lower limbs in two cases, and in the superior vena cava in two cases. One also had pulmonary emboli.

Liver function tests were abnormal in six patients with hepatocellular insufficiency in six cases, cholestasis in five cases and cytolysis in three cases. Mean serum levels of alanine aminotransferase and aspartate aminotransferase were 48 IU/L (range 16—97) and 35 IU/L (range 20—55), respectively. Mean levels of alkaline phosphatase and conjugated bilirubin were 329 IU/L (range 81—946) and 10 mg/L (range 2—37), respectively. Mean levels of prothrombin ratio and serum albumin were 55% (range 32—91) and 31 g/L (range 24—37), respectively. One patient had elevated creatinine.
Table 1  Principal features of Behçet’s disease associated with Budd–Chiari syndrome.
Principales caractéristiques de la maladie de Behçet associée au syndrome de Budd-Chiari.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Onset delay between Behçet’s disease and Budd–Chiari syndrome (years)</th>
<th>Oral ulcers</th>
<th>Genital ulcers</th>
<th>Pseudofolliculitis</th>
<th>Hypersensibility</th>
<th>Uveitis</th>
<th>Arthralgia</th>
<th>Neuro-Behçet</th>
<th>Venous thrombosis (not involving inferior vena cava and hepatic veins)</th>
<th>Arterial thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>27</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Superficial femoral vein</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>30</td>
<td>1</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Iliac vein</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>28</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Renal vein</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>34</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Superior vena cava</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>30</td>
<td>2</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Superior vena cava</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>30</td>
<td>2</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Superior vena cava</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>25</td>
<td>2</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Superior vena cava</td>
<td>0</td>
</tr>
</tbody>
</table>

+: present; 0: absent.

The Child–Pugh score was A in four cases and B in three others.

Plasma levels of proteins C and S as well as antithrombin were all within normal limits (between 70–130%, 60–140% and 80–120%, respectively). Screening for antibeta2-glycoprotein-1 and anticardiolipin antibodies was negative for all but one patient, who was positive for IgG anticardiolipin at a level of 37 IU/L; unfortunately, the test was not repeated.

Three patients screened positive for hepatitis B: two had “resolved” hepatitis; and one was probably an inactive AGHBs carrier, as he had normal transaminases and no significant hepatitis at liver biopsy. However, serum hepatitis B virus DNA was not assessed.

Upper flexible endoscopy was done in five cases and showed esophageal varices in two patients. A liver biopsy performed in one case demonstrated portal fibrosis associated with lymphocytic inflammatory infiltrate, without congestion.

All of our patients received anticoagulation therapy, and six had high-dose corticotherapy. Monthly cyclophosphamid intravenous pulses were given to two patients, and avoided in the case of the patient with chronic hepatitis B. In four cases, ascites required diuretics. One patient, who died of hepatic failure two months after BCS diagnosis, had not received any corticoid or immunosuppressive therapy.

Except for that patient, ascites improved in all cases. No patient had esophageal variceal bleeding or encephalopathy. No case of hepatocellular carcinoma was diagnosed, but this was not screened for. Mean time of follow-up was 43 months (range 2–143 months).

The clinical characteristics and type of vascular involvement in patients with BCS associated with BD are presented in Tables 1 and 2.

Discussion

Vascular disease occurs in approximately one-fourth of patients with BD and is called angio-Behçet [1,9]. There are three categories of vascular lesions: arterial occlusions; arterial aneurysms; and venous occlusions [1]. Venous occlusions are even more common in BD than arterial disorders, and have been observed in 7–46% of patients [9,10]. Superficial thrombophlebitis and deep vein thrombosis of the lower extremities are common, and have been observed in 30–40% of patients [11], whereas vena cava thrombosis is less frequent, occurring in 0.2–9% of patients [9]. Occlusion of the hepatic portion of the inferior vena cava, the major hepatic vein, or both, can lead to BCS. BD is an uncommon cause of BCS and, to our knowledge, only 55 cases of BD complicated with BCS have been published [1–5]. The rate of BCS in patients with BD is 2.8%, according to Bayraktar et al. [12], 0.3% according to Benamour et al. [13], 3.2% according to Urano et al. (autopsied cases) [14] and 1.3% according to Korkmaz et al. [5]. In our study, the rate was 3.2%. Thus, patients with BCS should always be screened for BD. The diagnosis can be difficult even in male patients from endemic countries, and use of the diagnostic criteria of the International Study Group of BD can be helpful in such cases [7].

In patients with BD, BCS is often related to inferior vena cava plus hepatic venous thrombosis. Only two patients (out of 14) in the study by Bayraktar et al. [12], 10 of the 51 cases in the literature [1–5] and one of our seven cases had BCS confined to the major hepatic veins. BCS with inferior vena cava occlusion displays distinctive features: clinical manifestations appear insidiously, ascites is usually absent and dilatation of the subcutaneous veins in the body trunk is more pronounced [15]. Moreover, the longstanding obs-
Budd–Chiari syndrome associated with Behçet’s disease

Table 2  Principal features of Budd–Chiari syndrome associated with Behçet’s disease. 
Principales caractéristiques du syndrome de Budd-Chiari associé à la maladie de Behçet.

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Refractory ascites</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lower-limb edema</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Enlarged spleen</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Collateral venous circulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>46</td>
<td>31</td>
<td>20</td>
<td>22</td>
<td>42</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>73</td>
<td>16</td>
<td>39</td>
<td>31</td>
<td>60</td>
<td>97</td>
<td>25</td>
</tr>
<tr>
<td>Alkaline phosphatases (IU/L)</td>
<td>103</td>
<td>418</td>
<td>81</td>
<td>317</td>
<td>206</td>
<td>234</td>
<td>946</td>
</tr>
<tr>
<td>Conjugated bilirubin (mg/L)</td>
<td>46</td>
<td>21</td>
<td>13</td>
<td>9.6</td>
<td>10</td>
<td>8.1</td>
<td>7</td>
</tr>
<tr>
<td>Child–Pugh score</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Esophageal varices on flexible endoscopy</td>
<td>+</td>
<td>0</td>
<td>ND</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Doppler ultrasonography</td>
<td>Hepatic vein, L; M; IVC</td>
<td>Hepatic vein, R; M; L; IVC</td>
<td>Hepatic vein, L; IVC</td>
<td>Hepatic vein; IVC</td>
<td>Hepatic vein; R; IVC</td>
<td>Hepatic vein; R; M; L; IVC</td>
<td>Hepatic vein, L; M</td>
</tr>
</tbody>
</table>

ND: not done; +: present; 0: absent; L: left; R: right; M: medial; IVC: inferior vena cava.

The obstruction to hepatic venous flow causes severe centrolobular fibrosis and predisposes to the development of hepatocellular carcinoma, which can occur in up to 40% of patients with inferior vena cava thrombosis [16]. Thus, patients are at risk of developing hepatocellular carcinoma if they have inferior vena cava involvement and longstanding obstruction, especially in those who also have chronic hepatitis B infection. Screening should be mandatory in such cases.

Treatment of BCS is medical, interventional and surgical. More than 80% of patients reported in the literature from 1959 to 1998 received medical treatment, consisting of various combinations of heparin, corticosteroid, thrombolytic therapy and colchicine [1]. As for cases with acute BCS, the results of medical treatment have been uniformly poor: 77% died after medical treatment, often within a month [1]. Thus, it was suggested by the authors that surgical portal decompression, when performed early in the course of BCS, has a better prognosis [1]. However, as recent data have failed to show a favorable impact of surgical portosystemic shunting on survival, many other treatments have been proposed instead [17]. Percutaneous angioplasty may be a safe and effective therapeutic modality when a short-length stenosis of the inferior vena cava or hepatic veins is found [4]. Recently, transjugular intrahepatic portosystemic shunt (TIPS) has been shown to be effective [17]. Liver transplantation offers the singular benefit of being curative [18]. Nevertheless, the indications for these different treatment modalities remain unclear.

When the course of BCS is not acute, as in our cases, the clinical picture is less severe and the prognosis is better. It is likely that patients with chronic BCS develop sufficient portal systemic collaterals that can decompress the obstructed liver [1,19]. In our study, six patients treated medically had a good prognosis possibly because none had BCS with an acute course and all had a collateral venous circulation. Only one patient died, and he had not received corticosteroid or immunosuppressive therapy.

Recently, Plessier et al. showed that excellent survival could be achieved in BCS when therapeutic procedures are introduced by order of increasing invasiveness, based on the response to previous treatment rather than on the severity of the patient’s condition [17]. Their therapeutic strategy consisted of four successive steps: beginning with anticoagulation and treatment of associated disease, symptomatic patients were considered for hepatic vein recanalization, then for TIPS and, finally, for liver transplantation. The absence of a complete response prompted the next procedure. Among our patients, only one failed to respond to the first step and it may be that we should have considered him for recanalization or TIPS, but those methods were not available at the time of his admission to hospital.

The cause of vascular thrombosis in BD is not currently known [12]. Because vasculitis is a major component of BD, we agree that hepatic vein vasculitis occurs in cases of BD and causes BCS [20,21]. Other conditions, such as factor V Leiden mutation, protein C/S deficiency and impaired fibrinolysis, may also be responsible for the occurrence of BCS in BD [5]. In 50% of BCS patients, more than one thrombophilic risk factor can be found [8]; however, in most reports of BD with BCS, coagulation parameters have not been studied. In the study by Korkmaz et al., three out of four patients had one or more factors predisposing to thrombosis [5]. In the
present report, only one patient had significant titers of anti-cardiolipin antibodies, but he was not reassessed, and the presence of factor V Leiden and prothrombin gene mutation were also not investigated.

Although patients with BCS and BD should be investigated for thrombophilic risk factors, we consider vasculitis to be the major cause of thrombosis. Thus, corticosteroids and immunosuppressive agents should be given as an adjunct to anticoagulant therapy, as in other forms of vasculitis [9].

**Conclusion**

The prevalence of BCS in patients with BD is 3.2%, confirming that BCS is not uncommon in BD. The inferior vena cava is frequently involved together with the hepatic veins and is frequently associated with other venous thromboses. The prognosis can be favorable with medical interventions, including anticoagulation, treatment of the vasculitis and the use of diuretics when required.

**References**


