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CASE REPORT

Budd-Chiari Syndrome in the Cirrhosis Stage Revealing Essential Thrombocythemia

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Abstract

Budd-Chiari syndrome (BCS) results from an obstruction of the hepatic venous drainage, from the hepatic venules up to the terminal part of the inferior vena cava.

A myeloproliferative syndrome, in particular an essential thrombocythemia (ET), is one of the most common causes (40-50%). The search for the Jak2 mutation facilitates haematological management. The diagnosis is made by Doppler ultrasound, supplemented by an MRI or CT scan. Support is based on early anti-coagulation, treatment of prothrombotic disease and complications of portal hypertension. Prognosis depends on the severity of the liver injury, the underlying prothrombotic condition and the hepatocellular carcinoma.

Through our observation we will try to highlight the physiopathological characteristics, diagnosis and therapeutic of BCS, at the stage of cirrhosis, associated with ET.

Keywords

Essential thrombocythemia, Budd-Chiari syndrome, Cirrhosis, Jak2 mutation, Myeloproliferative syndrome, Thrombosis

Introduction

Budd-Chiari syndrome (BCS) is the result of an obstruction of the supra-hepatic venous flow, occurring from the hepatic vein to the superior vena cava, which has multiple etiologies. The classic triad is clinically observed: Hepatomegaly, ascites and abdominal pain. Its management is based on a step-wise approach, depending on the clinical presentation, and includes different treatment from anticoagulation therapy up to Interventional Radiology techniques, such as transjugular intrahepatic portosystemic shunt (TIPS). If left untreated, it has got a high mortality rate.

SBC can be primary or secondary: in the latter case it can be caused by cystic compression of the veins, infiltration by a primary or secondary tumor, pregnancy or other rare causes. In its primary form, SBC is associated with thrombophilia such as that present in coagulation factor abnormalities (protein C and S, antithrombin III, factor V Leyden, factor II, etc.) or in overt or latent myelodysplastic syndromes (polycythemia vera, essential thrombocytosis, myelofibrosis, etc.) or diseases associated with coagulation disorders such as Behçet's disease or paroxysmal nocturnal hemoglobinuria. In a significant number of cases, the etiology remains undetermined.

Primary Budd-Chiari syndrome (BCS) is a rare disorder, most often secondary to prothrombotic conditions, the most common of which is Vaquez disease (VD) with a prevalence of 30-50% [1].

This association poses a diagnostic problem because abnormalities in the blood count of VD are masked by hypersplenism (so-called occult VD), and a therapeutic problem because of the management of anticoagulants in cirrhotic patients. The evolution is chronic, with a high rate of recurrence of thrombosis, which requires close long-term monitoring. The aim of our work is to highlight the diagnostic and therapeutic particularities of SBC at the stage of cirrhosis associated with PV

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through a medical observation collated at the internal medicine department of the Mohammed V Military Hospital in Rabat.

Observation

This is a 34-year-old patient, admitted to the Internal Medicine Department A of the Mohammed V Military Hospital for ascites assessment. The interrogation found no particular history, including no notion of tuberculosis contagion, no personal or family history of neoplasia and no risk factors for viral contagion. The history of his disease seems to go back to three months ago with the installation of a progressive abdominal distension, without externalized digestive hemorrhages, neither vomiting nor transit disorders, all evolving in a context of apyrexia and a slight weakening of the general state. The clinical examination on admission finds a patient in a good general condition, apyretic, with paroxysmal abdominal intense pain. Hemodynamic constants are stable: Cardiac frequency at 80 b/min, respiratory rate at 16 c/min, blood pressure is 130/70 mmHg. The abdomen is distended with diffuse dullness, splenomegaly and collateral venous circulation, but no hepatomegaly. Biologically, the blood count shows a hemoglobin level of 12.3 g/dl and a platelet level of 200,000/mm^3. Viral serologies B and C are negative. The rest of the assessment finds signs of hepatocellular insufficiency: Hypoalbuminemia, hypocholesterolemia and a low prothrombin level of 59% with decreased factor V. the rest of the lab results and the search for an underlying thrombophilia is shown in the table (Table 1).

Table 1: Laboratory results and the search for an underlying thrombophilia.

Laboratory testing	
ASAT (U/L)	58
ALAT (U/L)	81
Total bilirubin (mg/dL)	25
Albumine (g/dL)	29
Créatinine (µmol/L)	60
Prothrombin %	59
Hémoglobin (g/dL)	12.3
WG (10^9/L)	4.4
Platelets (10^9/L)	200
Child-Pugh grade	B
MELD score	10
Underlying thrombophilia testing	
Protein C deficiency	Neg
Proteine S deficiency	Neg
Anti-thrombine III deficiency	Neg
Behçet disease	No
Antiphospholipides syndrome	No
Oral contraception	_
Deep vein thrombosis	No
Malignancy	No
Family history	No

AST: Aspartate transaminase; ALT: Alanine aminotransferase; INR: International normalized ratio; MELD score: Model for end-stage liver disease score; Neg: Negative For these mutations; No: Means that the event or disease is not present.

Abdominal ultrasound confirms the presence of ascites. In which the ascitic protein concentration is 18 g/l (transsudative) and leukocytes levelof 30 elements/mm^3. The ultrasound also shows an aspect of chronic hepatopathy with splenomegaly. The esogastroduodenal endoscopy reveals stage III esophageal varices.

The Doppler ultrasound reveals thrombosis of the supra-hepatic veins and trunk in favor of a Budd-Chiari syndrome (BCS). The etiologic assessment of the BCS reveals an essential thrombocythemia, suspected by the data of the haemogram (a high level of platelets) and absence of other etiologies. Screening for the hypercoagulable state showed µmol/L, normal: A negative profile (lupus anticoagulant, protein C and protein S, factor V Leiden mutation, antithrombin III). Serum folate levels also decreased (3.3 ng/mL, normal: 5 to 22 ng/mL). Vitamin B-12 levels were normal (325 pg/mL, normal: 211 to 900 pg/mL). It's confirmed by an osteo-medullary biopsy showing an aspect evoking a myeloproliferative syndrome and by the presence of the V617F mutation of the JAK2 gene (Table 2). Thus, the diagnosis of BCS (at the cirrhosis stage) on essential thrombocythemia is retained. The patient is put on an anticoagulant treatment based on low molecular weight heparin relayed by anti-vitamins K., diuretics, alpha-blocker and hydrea.

Discussion

Myeloproliferative neoplasia is a group of acquired hematological diseases most often affecting adults, whose morbidity and mortality is largely due to hemostasis disorders. The most common complications are thromboses preferentially affecting the arterial territory, but also more atypical localizations such as thromboses of the splanchnic veins.

Table 2: WHO criteria for the diagnosis of essential thrombocythemia.

1- Thrombocytosis > 600 G / l persistent
2- Bone marrow biopsy:
Proliferation of the megakaryocytic line with high proportion of large mature megakaryocytes
3- No index of:
• Polycythemia vera
• Chronic myelogenous leukemia
• Osteomyelofibrosis
• Myelodysplastic syndrome
• Reactive thrombocytosis

Myeloproliferative syndromes (MPS) (chronic myeloid leukemia, Vaquez disease, essential thrombocythemia, primary myelofibrosis) are clonal hematological malignancies derived from the transformation and autonomous multiplication of a hematopoietic stem cell. BCR-ABL negative myeloproliferative syndromes (MPS), excluding chronic myeloid leukemia (CML), classically include the following three pathologies: Essential thrombocythemia (ET), Vaquez disease (VD) and primary myelofibrosis (PMM) [2]. The JAK2 V617F mutation is the molecular event responsible for 95% of Vaquez disease, 50% of essential thrombocythemia and 50% of primary myelofibrosis [3]. The JAK2 V617F mutation is the molecular event responsible for many Vaquez diseases, essential thrombocythemias and primary myelofibrosis, and it assists the clinician in the diagnosis of BCR-ABL negative SMPs.

Thromboses are more frequent and often more severe than bleeding events and can also be a mode of entry into the disease and allow diagnosis. Moreover, they represent the main complication of NMPs and are responsible for significant morbidity and mortality: 45% of deaths are due to cardiovascular causes [4]. Indeed, the prevalence of thrombosis at diagnosis is of the order of 30% for VD, 20% for TE and 10% for MFP [5,6].

A recent cohort study of more than 9,000 patients with NMPs and 35,000 controls followed over 20 years found a higher risk of thrombosis (both arterial and venous) in patients with NMPs compared to the general population [7].

The clinical features of BCS are myriad and may range from asymptomatic disease early in the course, particularly in patients with involvement of one hepatic vein, to signs of chronic liver disease with ascites and other signs of hepatic dysfunction. Thus, an early diagnosis of this entity relies on radiological evaluation. The non-invasive modalities for diagnosis of BCS are Doppler ultrasound, CT, and MRI. MRI showed the highest sensitivity, and CT showed the highest specificity for the diagnosis of BCS [8].

Atypically localized thrombosis, particularly intra-abdominal thrombosis, may therefore be indicative of an NMP, which is the main cause: In fact, 30-50% of Budd-Chiari syndromes and 15-30% of portal vein thrombosis are associated with an NMP [9]. Predisposing factors include, among others, inherited or acquired hypercoagulability and especially myeloproliferative diseases, as in our case [10].

Primary myeloproliferative disorders are the leading cause of BCS. However, 25% of patients may have more than one etiological factor responsible for the hypercoagulable state in BCS.

The pathophysiology of thrombosis is complex and multifactorial, involving different actors such as blood cells, endothelium and flow conditions. Erythrocytes show quantitative and qualitative changes.

Table 3: IPSET-thrombosis Score according to Barbui, et al., Blood 2011.

Risk factors	Score
• **Age over 60 years**	1
• **Cardiovascular risk factors**	1
• **History of thrombosis**	2
• **JAK2 V617F Mutation**	2

Low risks (total score = 0-1, annual incidence of thrombosis 0.5 à 1.19%), intermediate (total score = 2, annual incidence of thrombosis 1.76 à 2.35%) and high (total score ≥ 3, annual incidence of thrombosis 2.28 à 4.88%).

For essential thrombocythemia, the items that retained value in a multivariate study were combined into a proposed score, the International Prognostic Score for Essential Thrombocythemia (IPSET thrombosis) (Table 3) [11]. This score takes into account the two recognized major risk factors; age over 60 years and history of thrombotic events, as well as the presence of the JAK2V617F mutation and cardiovascular risk factors (tobacco, hypertension and diabetes). It stratifies the risk into three categories: low (total score = 0-1), intermediate (total score = 2) and high (total score ≥ 3), associated with thrombosis incidences of 0.5 to 1.19%, 1.76 to 2.35% and 2.28 to 4.88% of events/year respectively.

The etiologies of primary BCS are multiple and varied, dominated by myeloproliferative syndromes, present in 50% of carriers of primary BCS [1]. The myeloproliferative syndrome most frequently responsible for BCS is VD. Essential thrombocythemia may also be involved and chronic myeloid leukemia is only rarely implicated in the occurrence of BCS. After myeloproliferative syndromes, the most frequently cited pathology in the genesis of BCS is the primary phospholipid antibody syndrome (PAS). Other coagulation disorders (Table 4) such as an isolated deficiency of protein C, protein S, antithrombin III, or a mutation of factor V Leiden may be implicated [12]. Regarding the case of our patient, the SAPL test was negative as well as other thrombophilia factors. Other causes are more rarely incriminated: Paroxysmal nocturnal hemoglobinuria, Behçet's disease, celiac disease, sarcoidosis or a hypereosinophilia syndrome. The notion that BCS is a multifactorial disease should be emphasized, since two thrombogenic factors are considered to be present in 50% of BCS [13]. The role of estrogen-progestogens has been highlighted (this has been proven with high estrogen-dose contraceptives) and a thrombogenic associated cause must be sought.

Platelets also show quantitative and qualitative changes. However, an increase in platelet count during NMPs is not predictive of the occurrence of a thrombotic event, as no correlation has been demonstrated between the level of thrombocytosis and thrombotic risk [14].

NMPs also exhibit a state of hypercoagulability

Table 4: Hypercoagulable states can cause Budd Chiari syndrome.

Acquired
• Myeloproliferative disorders
• Antiphospholipid syndrome
• Hyperhomocysteinaemia
• Paroxysmal nocturnal haemoglobinuria
• Malignancy
• Pregnancy
• Use of oral contraceptives C
Inherited
• Factor V Leiden mutation
• Prothrombin gene mutation
• Antithrombin III deficiency
• Protein C deficiency
• Protein S deficiency
Tumour invasion
• Hepatocellular carcinoma
• Renal cell carcinoma
• Adrenal carcinoma
Idiopathic
Other (uncommon causes) Autre (causes rares)
• Behçet's syndrome
• Inferior vena caval webs
• Aspergillosis
• Hydatid disease
• Traumatisme
• Dacarbazine therapy
• Sarcoidosis

demonstrated by increased thrombin generation in TEs. This excessive activation of coagulation is partly explained by an increase in microparticles of platelet and endothelial origin [15].

These microparticles contribute to the occurrence of thrombosis by providing anionic phospholipids and tissue factor. In addition to that, microparticles have the ability to increase COX2 expression and thus platelet activation and to stimulate the release of pro-inflammatory cytokines (IL6 and IL8) and adhesion molecules. The hypercoagulable state can also be explained by resistance to activated protein C, which is more common in TE patients with a history of thrombotic events and in JAK2 V617F mutated patients [16].

Complications of Budd-Chiari syndrome are mostly related to underlying conditions and degree of liver failure. In general, untreated Budd-Chiari syndrome can lead to the following [17]:

Hepatic encephalopathy, Variceal hemorrhage, Hepatorenal syndrome, Portal hypertension, Bacterial peritonitis in the presence of ascites and Heptocellular carcinoma.

Factors contributing to a bad prognosis [17]:

Involvement of all three hepatic veins and/or portal vein, Presence of ascites, Older age at the time of presentation and High Child-Pugh score Chronic disease at presentation.

Conclusion

Primary Budd Chiari syndrome (BCS) is a rare disorder, most often secondary to prothrombotic conditions, especially TE.

The association between BCS and TE is not rare and requires the search for the JAK2 mutation. Treatment is based on anticoagulants, which are difficult to manage in cirrhotic patients.

The prognosis depends on one hand on the complications of cirrhosis and on the other hand on the risks of malignant transformation.

Conflicts of Interest

The authors declare no conflict of interest, financial or otherwise.

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