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Case Report

Budd-Chiari Syndrome in Myeloproliferative Neoplasms: Case Report and Literature Review

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Abstract

Budd-Chiari Syndrome (BCS) represents a rare yet clinically significant manifestation of hepatic venous obstruction, often associated with myeloproliferative neoplasms (MPNs). This abstract synthesizes a clinical case and discussion focusing on BCS within the context of MPNs, emphasizing diagnostic challenges, treatment modalities, and prognostic implications.

The presented case involves a 65-year-old patient exhibiting symptoms of ascites and abdominal pain, leading to the diagnosis of BCS secondary to MPNs. Clinical examination revealed jaundice, splenomegaly, and abnormal laboratory findings indicative of hepatocellular insufficiency. Imaging studies confirmed portal thrombosis and inferior mesenteric vein thrombosis, characteristic of BCS. Molecular analysis revealed the presence of the JAK2 V617F mutation, confirming an underlying MPN etiology.

Discussion highlights the intricate relationship between BCS and MPNs, underscoring the importance of early recognition and targeted management. Thrombotic complications in MPNs, including BCS, stem from complex pathophysiological mechanisms involving endothelial damage, clot formation, and genetic mutations. Diagnosis of BCS relies on imaging modalities such as Doppler ultrasound and CT angiography, while genetic testing aids in identifying underlying MPNs.

Treatment strategies encompass a multidisciplinary approach aimed at preventing thrombosis recurrence and managing complications. Anticoagulation, cytoreductive therapy, and interventional procedures like transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation constitute mainstays in BCS management. However, prognosis remains guarded, especially in patients with advanced disease or thromboembolic events.

The association between MPNs and BCS underscores the need for tailored counseling and vigilant monitoring in affected individuals. Adherence to updated guidelines and multidisciplinary collaboration are imperative for optimizing patient outcomes. Furthermore, recognizing MPNs as potential underlying causes of BCS is paramount, prompting active investigation and genetic testing in affected patients.

In conclusion, this abstract elucidates the complex interplay between BCS and MPNs, highlighting diagnostic intricacies, treatment modalities, and prognostic considerations. Comprehensive evaluation, timely intervention, and individualized care are pivotal in mitigating the impact of these rare yet formidable conditions on patient health and well-being.

Keywords: *Budd-Chiari Syndrome (BCS); Transjugular Intrahepatic Portosystemic Shunt (TIPS); Myeloproliferative Neoplasms (MPNs); Philadelphia-Negative Chromosome (Ph1neg); Polycythemia de Vaquez (PV); Thrombocythemia (ET); Primary Myelofibrosis (PD)*

Introduction

Myeloproliferative neoplasms (MPNs) are defined as clonal disorders of hematopoietic stem cells in which exaggerated production of differentiated myeloid cells in the terminal phase occurs. The "classic" Philadelphia-negative chromosome (Ph1neg) myeloproliferative neoplasms (MPNs) include Polycythemia de Vaquez (PV), essential thrombocythemia (ET), and primary myelofibrosis (PD). Philadelphia NMPs have a propensity to develop thrombotic complications [1-3]. In MPNs, thrombosis can occur in unusual sites, e.g. portal or hepatic veins, placenta, or cerebral sinuses. The pathogenesis of thrombotic events in MPNs is complex and requires a complex mechanism involving endothelial damage, stasis, elevated leukocyte adhesion, integrins, neutrophil extracellular traps (NETs), somatic mutations (e.g. the V617F point mutation in the JAK2 gene), microparticles, circulating endothelial cells, and other factors, to name a few [4,5]. Here, through a clinical case, we review the available data on Budd-Chiari syndrome (SBS) in Philadelphia NMP negative, with a particular focus on its risk factors, classification, clinical presentation, diagnosis, and management.

Observation

This is a 65-year-old patient, admitted to the gastroenterology department of the IBN Rochd University Hospital in Casablanca for assessment of ascites with abdominal pain. The examination did not find any particular history, including no notion of tuberculosis infection, no personal or family history of neoplasia, and no risk factors for viral contagion. The history of his illness seems to date back three months with the appearance of progressive abdominal distension, without externalized digestive bleeding, vomiting or transit disorders, all evolving in a context of apyrexia and a weakening of the general condition.

Clinical examination revealed a patient PS=3, jaundice and reporting moderate epigastric pain. The hemodynamic constants are correct: Heart rate 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 complete blood count shows a haemoglobin (Hb) level of 19.3 g/dl, red blood cells (Gr) at 8 million, leukocytes at 17400/mm^3 predominant PNN with lymphopenia at 850/mm^3 and a platelet count of 503,000/mm^3. Serologies B and C are negative. The remainder of the assessment found evidence of hepatocellular insufficiency: Hypoalbuminemia, hypocholesterolemia, and a low prothrombin level of 59% with a decrease in factor V. The rest of the laboratory findings and the search for underlying thrombophilia are presented in table 1.

Biological Tests	
ASAT (U/L)	92
ALT (U/L)	81
Bilirubin total (mg/dL)	78
Album (g/dL)	24
Creatinine (µmol/L)	122
Prothrombin %	< 10%
Hemoglobin (g/dL)	19.4
Hematocrit %	60
GB (109/L)	17.14
Platelets (109/L)	503
CHILD-Pugh	C14
REPORT score	27
Thrombophilia assessment	

Protein C deficiency	Negative
Protein S deficiency	Negative
Antithrombin III deficiency	Negative
Antipholipid Syndrome	Negative
Behcet's disease	Negative
Mutation JAK2	Positive
Mutation fact V de Leiden	Negative
Mutation MTHFR	Negative

Table 1: *Laboratory results and thrombophilia assessment.*

Abdominal ultrasound confirms the presence of ascites. In which the protein concentration is 9 g/l (Transudative). Ultrasound also shows an appearance of chronic liver disease with the presence of portal thrombosis. Esophageal endoscopy shows the absence of esophageal varices.

Abdominal CT angiography reveals a thrombosis of the inferior mesenteric vein (VMI) with absence of opacification of the suprahepatic veins (VSH) in favor of Budd-Chiari syndrome (SBC). The etiological assessment of the SBC reveals Vaquez's disease, suspected by the blood count data (high levels of hemoglobin and red blood cells) and absence of other etiologies. The diagnosis was confirmed by the presence of the V617F mutation in the JAK2 gene and an osteomedullary biopsy showing hyperplastic rich marrow with hyperplasia of the megakaryocytic lineage (Table 2).

Major Criteria (M)	**Man**	**Wife**
M1 Hemoglobin (Hb), Hematocrit (Hte)	Hb > 16,5 g/dl You hte > 49% or increased blood mass (> 25% above expected normal value)	Hb > 16 g/dl You hte > 48% or increased blood mass (> 25% above expected normal value)
M2 Osteomedullary biopsy	Hypercellularity for age with excessive proliferation of the 3 myeloid lineages (panmyeloses)	
M3 Mutation JAK2	V617F (exon 14) w exon 12	
Minor Criterion (m)		
Serum EPO	Normal or subnormal serum assay	

Table 2: *Diagnosis of polycythemia de Vaquez according to the criteria of the WHO 2017.*

The 2017 WHO diagnostic criteria are M1 + M2 + M3 or M1 + M3 + m if Hb > 18.5 g/dL (or Hte > 55.5%) in men or Hb > 16.5 g/dL (Hte > 49.5%) in women.

Treatment with low-molecular-weight heparin (LMWH) was initiated, followed by vitamin K antagonists and hydroxycarbamide.

Despite this therapeutic attitude, the prognosis was unfortunate and the patient died 15 days later.

Discussion

Budd-Chiari syndrome results from obstruction of hepatic venous drainage from the hepatic venules to the terminal part of the inferior vena cava, regardless of the cause of the obstruction; It is primary when it is caused by thrombosis or by its fibrous, secondary sequelae, when the vein is invaded or compressed by a tumor or parasitic obstruction.

One or more thrombogenic conditions are usually present; The most common of these is the presence of a myeloproliferative syndrome. The main complications are ascites, more rarely hepatocellular insufficiency, and rupture of oesophageal varices, hepatocellular carcinoma, thrombotic recurrences and complications of the causative disease. A quarter of patients do not suffer from any clinical manifestation at diagnosis. There is often a diagnostic error.

Diagnosis is usually made by Doppler ultrasound, liver CT or magnetic resonance imaging, either by showing inter-suprahepatic or cavohepatic or cava collateral circulation, or lumen-obstructing material from the hepatic or cava veins in the territory of hepatic drainage.

The natural history is poorly understood, and mortality is higher in the early stages of the disease. The first stage of treatment is aimed at preventing the recurrence or spread of thrombosis with anticoagulants. The second step is to control ascites and gastrointestinal bleeding with the non-specific measures usually used in portal hypertension, and to treat localized venous lesions with vein angioplasty when feasible. When symptoms are not controlled by these different treatments, TIPS is attempted. If this fails, or in the case of hepatocellular carcinoma, liver transplantation remains the standard treatment.

Up to 50 percent of all cases of Budd-Chiari syndrome may be due to an underlying chronic myeloproliferative disorder (e.g. essential polycythemia, essential thrombocythemia, agnogenic myeloid metaplasia) and an accompanying hypercoagulable state. Peripheral blood signs of myeloproliferation may not be present if portal hypertension, splenomegaly, and hypersplenic state accompany Budd-Chiari syndrome.

Myeloproliferative syndromes (occult or overt) are often associated with hypercoagulability [6,7]. In one of the largest published series (involving 237 patients evaluated at four centers between 1984 and 2001), 23% had overt myeloproliferative disorder (polycythemia vera in 45 patients and essential thrombocytosis in 9 patients). In another large series, 49 percent of the 103 patients tested had a myeloproliferative disorder, the most common of which was polycythemia de Vaquez [6,8].

Spontaneous erythroid colony formation in the presence of low serum erythropoietin levels results in increased growth of megakaryocyte colonies, and clonal karyotypic abnormalities have all been reported in patients with Budd-Chiari syndrome due to MPNs and in some so-called “idiopathic” cases of Budd-Chiari syndrome, suggesting the presence of occult myeloproliferative syndrome in these individuals [9-13]. In one study, for example, spontaneous formation of endogenous erythroid colonies *in vitro* and/or on bone marrow biopsies suggested that primary myeloproliferative disorder was present in 78% of these patients [14].

Mutations in the tyrosine kinase JAK2 (V617F) have been described in 26 - 59 percent of patients with Budd-Chiari syndrome, many of whom had negative standard test results for myeloproliferative disorders [6,7,13,15]. A JAK2 mutation is present in almost all patients with essential polycythemia and about 50 percent of patients with essential thrombocythemia or myelofibrosis.

There is some evidence to suggest that the liver may produce erythropoietin during the acute phase of Budd-Chiari syndrome. Such a change could contribute to the formation of spontaneous erythroid colonies in cultured bone marrow or peripheral blood mononuclear cells demonstrated in these patients [16].

Anticoagulation should be initiated as soon as possible in most patients to prevent the spread of the clot, provided there are no contraindications. However, the risk of anticoagulation should be considered, especially in patients with bleeding complications or varicose veins. Before starting anticoagulation, we perform an upper endoscopy to screen for varicose veins. We administer anticoagulation to patients with a history of gastrointestinal variceal bleeding or varicose veins who are at increased risk of bleeding (especially in those with cirrhosis) only if adequate prophylactic measures to prevent recurrent bleeding can be implemented. We prefer the use of a beta-blocker to esophageal varices ligation (EVL) for prophylaxis in these patients due to the risk of bleeding due to pressure ulcer falls.

We prefer to treat with low molecular weight heparin as a first step. In selected patients, such as those at high risk of bleeding or with renal impairment, we will check for anti-factor Xa activity, targeting it between 0.5 and 0.8 international units/mL. We also start oral treatment with a vitamin K antagonist (e.g. warfarin) in patients. Once the international normalized ratio is between two and three, we stop low-molecular-weight heparin. Anticoagulation is continued indefinitely unless there is a major contraindication, complication, or obstruction due to a corrected anatomical cause.

However, sufficient recanalization of occluded vessels or development of adequate collateral circulation often do not occur in patients treated with anticoagulation alone. The use of anticoagulation as the sole treatment for Budd-Chiari syndrome is generally reserved for patients with chronic or subacute Budd-Chiari syndrome and well-compensated liver disease at the time of presentation; However, even in these patients, additional measures to decompress the liver should be considered (especially if they are not candidates for liver transplantation) in an attempt to delay the progression of liver disease; as well as patients in whom no other therapy is feasible [6].

For patients with acute Budd-Chiari syndrome who present with a well-defined clot less than three to four weeks of age, thrombolytic therapy rather than anticoagulant monotherapy (Grade 2C) is suggested. We avoid the use of thrombolytic agents in patients with an extensive clot involving the intrahepatic vena cava and hepatic veins, or in patients with a clot of unknown age.

For patients with acute or subacute Budd-Chiari syndrome who are symptomatic and are not candidates for thrombolytic therapy, we suggest angioplasty and stenting with anticoagulation rather than anticoagulant monotherapy, provided that a venous obstruction amenable to percutaneous angioplasty and stenting is visualized radiologically.

Treatment options for patients with acute or subacute Budd-Chiari syndrome who fail to improve with other treatments include transjugular intrahepatic systemic porto shunt (TIPS), surgical shunt, and liver transplantation. TIPS placement and liver transplantation may also be options for patients with cirrhosis who develop complications of cirrhosis.

Management of PV is guided by a risk-based approach based on age (i.e. ≤ 60 years versus > 60 years) and history of previous thrombosis. Patients aged ≤ 60 years without a history of thrombosis are classified as low risk; all others are considered high-risk.

Phlebotomy is the mainstay of red blood cell mass management in PV. For all patients with PV, it is recommended to maintain a hematocrit < 45 percent, rather than higher levels (Grade 1A). For all patients except those with a contraindication (e.g. acquired von Willbrand syndrome (vWS), low-dose aspirin is recommended. For patients at high risk of PV (> 60 years and/or history of thrombosis), phlebotomy combined with cytoreductive therapy primarily hydroxyurea, rather than phlebotomy alone, is recommended.

Median survival of untreated symptomatic patients with PV has been estimated to be 18 months, but survival is at least 13 years in treated patients. Nevertheless, the overall survival of patients treated with PV is lower than that of a normal population of the same age and sex [17-21].

Thromboembolic events are the leading cause of morbidity and mortality in PV. Older age and history of thrombosis are predictors of thromboembolic risk in PV [17,22-24]. Other risk factors, including leukocytosis and thrombocytosis, are less conclusively associated with vascular events in PV.

In our patient, the prognosis was guarded due to the combination of all the above-mentioned factors, as well as the presence of a bilateral pulmonary embolism.

Conclusion

Although SBS and MPNs are rare disorders, BCS can develop as part of MPN. In this patient population, individualized and distinctive counseling as well as multidisciplinary monitoring and treatment strategies are essential to achieve the best possible outcomes. Individuals with MPN should be managed according to the most up-to-date guidelines to avoid the occurrence of SBC, whereas a diagnosis of SBC should warrant active research into the potential diagnosis of MPN.

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