International Journal of Academic Health and Medical Research (IJAHMR)
ISSN: 2643-9824
Vol. 7 Issue 2, February - 2023, Pages: 56-59

Cirrhosis on Budd-Chiari syndrome revealing a Polycythemia Vera: A case report

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Abstract: Introduction*: Polycythemia Vera (PV) is the most common etiology of primary Budd-Chiari syndrome (BCS), with a prevalence of 30%-50%. This association poses a diagnostic problem, because the abnormalities of the hemogram during PV are masked by hypersplenism, and a therapeutic problem due to the management of anticoagulants in cirrhotic patients. The aim of this work is to demonstrate the diagnostic and therapeutic particularities of SBC at the stage of cirrhosis associated with PV through a medical observation collected in the hepato-gastroenterology department of University Hospital , FEZ.* ***Observation****: This is a 42 year old man, with no medical past history, admitted to our department for exploration of ascitis. The underlying etiology was a cirrhosis on BCS, confirmed by the visualization of thrombosis of the right and median hepatic veins on abdominal angio CT scan . The etiological investigation of the BCS revealing PV, suspected on the results of the haemogram and confirmed by an osteo-medullary biopsy and by the presence of the V617F mutation of the JAK 2 gene by allele-specific PCR. An anticoagulant treatment, based on low molecular weight heparin and anti-vitamins K, was started and the patient was treated with cytoreductive therapy with satisfactory clinico-biological evolution.* ***Conclusion****: Primary SBC is often due to PV, but in the majority of cases, the haemogram is not characteristic, mainly because of the associated hypersplenism, therefore the systematic search for the JAK2 mutation. Treatment is based essentially on anticoagulants, which require special management in cirrhotic patients because of the risk of bleeding due to portal hypertension.*

Keywords: Polycythemmia Vera, JAK2 mutation, Budd-chiari syndrome, cirrhosis

Introduction :

Primary Budd-Chiari syndrome (BCS) is a liver disease characterized by hepatic venous flow obstruction in the vascular space between the hepatic venules and the junction between the inferior vena cava and the right atrium, thus excluding upstream (sinusoidal obstruction syndrome) and downstream (cardiac causes) causes. It is a rare entity most often secondary to pro-thrombotic conditions, the most frequent of which is Polycythemia Vera (PV) with a prevalence of 30 to 50% [1].

This association poses a diagnostic problem, because the abnormalities of the PV hemogram are masked by hypersplenism ,and a therapeutic problem because of the management of anticoagulants in cirrhotic patients. The course is chronic, with a high rate of recurrence of thrombosis, requiring close long-term monitoring. The prognosis depends on the one hand on the complications of cirrhosis and on the other hand on the risks of malignant transformation during PV [1].

The aim of the present observation, report the diagnostic and therapeutic particularities of SBC at the stage of cirrhosis associated with PV .

Observation :

A 42 years old man was admitted to our department for exploration of ascitis associated with slowing down psychomotor, with no past medical history.

The history of his disease goes back to 4 months ago with a progressive abdominal distension, associated with a subicterus, without external gastro intestinal bleeding, vomiting or transit disorders, all in a context of apyrexia and conservation of the general state.
The clinical examination found a conscious patient, slowed down, no asterixis, sub icteric, apyretic, with erythrosis of the face and edema of the lower limbs reaching the knees. The hemodynamic parameters were stable: heart rate at 67b/min, respiratory rate at 16c/min, blood pressure was 120/60 mmHg. The abdomen was distended with diffuse dullness, collateral venous circulation, splenomegaly without hepatomegaly. Cardiovascular and pleuropulmonary examination without abnormalities, lymph node areas were free.
The biological test revealed a red blood cell count of 7.65 . 10/ml, a hemoglobin level of 17.5 g/dl , a platelet level of 266,000/mm3 and a white blood cell level of 4540/mm3 in the blood count, a prothrombin level of 72%, a correct renal function with a creatinine

level of 11mg/l and urea of 0.4mg/l. The hepatic test showed a slight cytolysis predominantly on Aspartate amino transferase (ASAT) at 2 times the upper normal limit (ULN), Alanine amino transferase (ALAT) at 1.6 ULN, Gamma glutamyl transferase (GGT) at 4 ULN and Alkaline phosphatase (PAL) at 1.7 ULN. Total hyperbiliribinemia at 25mg/dl with a direct predominance at 15mg/dl. The blood ionogram showed a natremia 135 mmol/l and kalemia 3.7 mmol/l .

Abdominal ultrasound showed a dysmorphic and heterogeneous structure of liver, suprahepatic veins were not visualized , a splenomegaly with abundant ascitis. Abdominal and pelvic angiotomodensitometry (CT) confirmed the BCS: Thrombosis of the right and middle VSH.

The ascitis examination showed a protid rate of 18 g/l (transudative), leucocyte rate of 120 elements/mm3, predominantly lymphocytic (66%).
The upper gastro intestinal endoscopy did not reveal a oesophageal or gastric varices.

Etiological investigation of the chronic hepatopathy revealed: HBsAg, anti HBs antibodies, anti HBc antibodies negative, hepatitis C serology negative, a correct rate of: cholesterol at 1.2 g/l, HDL cholesterol at 0.5 g/l, LDL cholesterol at 1.3 g/l and triglycerides at 1.6 g/l, a correct glycaemia at 0. 9 g/l with glycated hemoglobin at 5.6%. Protein elecrophoresis (PPE) showed a beta-gamma block in favor of hepatic cirrhosis, the autoimmune check-up was negative. The ferritin level was normal at 125 ng/ml, with a transferrin saturation coefficient of 30%.

A PV was suspected based on: a high rate of red blood cells to 7.65.10/ml, an increased hematocrit to 52%, with a high hemoglobin rate to 17. 5 g/dl, and confirmed by an osteomedullary biopsy showing a myeloproliferative syndrome with pan-meyloid hypercellularity, particularly megakaryocytic, and the detection of the V617F mutation of the JAK 2 gene by allele-specific PCR.

In all , the diagnosis of BCS (at the stage of cirrhosis) on PV was confirmed . The patient was treated by a low molecular weight heparin anticoagulant, followed by anti-vitamin K and a hydroxyurea-based cytoreductive treatment.
The evolution under treatment was marked by a decrease in the hemoglobin level to 14 g/dl and hematocrit to 35%.
The upper endoscopy showed stage I esophageal varices without red signs, the patient was made on beta blockers.

Discussion :

Myeloproliferative syndromes (MPS) are the first cause of primary SBC with a prevalence of 30-50% [1], this prevalence is much higher than in the general population where it is estimated at 0.2% [2].
The most common SMP causing SBC is PV, essential thrombocythemia (ET) may also be responsible and chronic myeloid leukemia (CML) is only rarely implicated in the occurrence of BCS [3].

Antiphospholipid antibody syndrome is the second most common cause of primary SBC after SMP. Other coagulation disorders such as isolated deficiency of protein C, protein S, and antithrombin III, or a mutation of factor V Leiden can be incriminated [4]. Other rare causes of BCS have been found: paroxysmal nocturnal hemoglobinuria, Behçet's disease, caeliac disease, sarcoidosis, or a hypereosinophilia syndrome [5] .
In MPS and particularly in PV, arterial and venous thrombosis are major complications. A particularity to be noted is the occurrence of thrombosis in so-called unusual territories, such as cerebral venous thrombosis or venous thrombosis of the splanchnic, suprahepatic and portal system [6]. Therefore, the search for a latent myeloproliferative syndrome is systematic in the exploration of a portal or hepatic venous thrombosis in the absence of an identifiable obvious cause.

The diagnosis of PV is based on a combination of many criteria, the latest published classification being that of WHO 2007 [7] :

Major criteria
1. Hemoglobin >18.5 g/dL in men, >16.5 g/dL in women, or other evidence of increased red cell volume*
2. Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation

Minor criteria
1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation *in vitro*

*Hemoglobin or hematocrit greater than 99th percentile of method-specific reference range for age, gender, altitude of residence or hemoglobin greater than 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from an individual's baseline value that can not be attributed to correction of iron deficiency, or elevated red cell mass greater than 25% above mean normal predicted value. *Modified from Tefferi* et al.,*2007.*[7]

The search for the JAK2 V617F mutation, by allele-specific PCR, helps in the diagnosis; it is noted in 61 % to 97% of patients with polycythemia Vaquez. This mutation in JAK2 is the primary molecular event leading to the development of PV. Allele-specific PCR testing for the JAK2 V617f mutation should be performed routinely in the etiological workup of BCS without an obvious cause [8].

Therapeutically, the prescription of aspirin in isolated PV prevents thromboembolic complications. The occurrence of thrombosis during PV, and in particular for SBC, requires the initiation of anticoagulant treatment with low-molecular-weight heparin rapidly followed by a vitamin K antagonist. The risk of high thrombotic recurrence is thus significantly reduced. The benefits of lifelong anticoagulation outweigh the risk of bleeding even in the presence of portal hypertension, for patients receiving primary or secondary prophylaxis of portal hypertension-related GI bleeding [9, 10].

Polycythemia vera treatment is largely dependent on the age of the patient, risk of thrombosis and progressive development of thrombocytosis or splenomegaly, indexes of disease evolution [11].
The first therapeutic approach is still phlebotomy to maintain hematocrit consistently below 45%, the approach based exclusively on phlebotomies is indicated only in patients at low risk of thrombosis (age<60 years and no history of previous thrombotic events) [12].
In those patients in whom phlebotomy alone is not able to prevent complications, myelosuppressive therapy should be started as soon as possible. In sub jects older than 70 years the use of radiophosphorus and busulfan or other alkylating agents is strongly advised, in combination with aspirin if the patient is at high thrombotic risk [13].
In all other patients (age<70 years), cytoreductive therapy with hydroxyurea should be considered. Many studies evaluated the efficacy and safety of this drug, compared both to untreated patients and those treated with alkylating agents, underlining the significant reduction in thrombosis risk (5.6% vs 21.6%) and increased survival.Nevertheless, many doubts remain about the proven leukemogenicity and myelodysplastic potential of hydroxyurea [12-14].

The prognosis of SBC related to a PV myeloproliferative syndrome is related to:
- the risk of transformation of this hemopathy into acute myeloid leukemia or myelofibrosis, this risk is about 15% at 10 years of evolution ;
- as well as to the specific complications of cirrhosis and the development of hepatocellular carcinoma, particularly in patients with associated obstruction of the inferior vena cava [12]. However, many nodules that appear in chronic SBC correspond to lesions that are radiologically and histologically close to focal nodular hyperplasia [13].

Conclusion :
Therapeutic management of PV must be multidisciplinary, involving hematology, gastroenterology and cardiology. The prognosis of this affection has improved significantly in recent years.

Complications are related to cirrhosis when it exists and in particular to hepatocellular carcinoma as well as to PV and in particular to its transformation into acute myeloid leukemia or myelofibrosis.

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