

Budd-chiari syndrome at diagnosis in polycythemia vera – case report

I. VOICAN¹, A.M. VLADAREANU¹, M. BEGU¹, C. DOBREA², V. VASILACHE¹, D. CISLEANU¹, H. BUMBEA¹, A. ILEA³, M. DERVESTEANU¹, S. RADESI¹, M. ONISAI¹

¹Haematology Clinic, University Emergency Hospital, Bucharest

²Victor Babes National Institute

³Ritus Biotech, Codlea Brasov

ABSTRACT

Among all BCR-ABL negative chronic myeloproliferative diseases, Polycythemia Vera and Essential Thrombocythemia are most frequently associated with thrombotic events, often with unusual locations.

Hereby we present the case of a patient concomitantly diagnosed with suprahepatic veins thrombosis and PV, where the clinical-pathological picture corroborated with paraclinical data raised the problem of a differential diagnosis with Mosse Syndrome. Rapid initiation of an intense cytostatic and anticoagulant treatment, together with pathogenic and symptomatic measures regarding hepatic cirrhosis insured a favorable evolution of the disease, with normalization of hematological parameters, disappearance of phenomenon of liver failure and diminution of the thrombotic process.

Key words: polycythemia vera, suprahepatic veins thrombosis, anticoagulant

Budd-Chiari Syndrome (BCS) is a rare disease primarily determined by the hepatic veins thrombosis at different levels: hepatic venules, suprahepatic veins, inferior vena cava or right atrium (1). Hepatic veins obstruction determines an increase in hepatic sinusoids pressure and portal hypertension. At the beginning there is a decrease in the hepatic perfusion, able to induce portal thrombosis. Venous stasis and congestion determine hypoxic alterations of the nearby parenchyma and release of free radicals, centrilobular liver necrosis, progressive fibrosis, nodular regeneration hyperplasia and, finally, hepatic cirrhosis. Development of Porto-systemic shunts or of collateral portal circulation could improve hepatic function.

Clinical manifestations of BCS depend on the rapidity and extension of the venous occlusion,

the most common way of presentation being subacute form; in the acute form, that implies the occlusion of all major hepatic veins, the symptoms appear relatively quickly, consisting in abdominal pain, jaundice, ascitis and hepatic necrosis. Thrombosis extension to the inferior vena cava expresses itself clinical through collateral venous circulation on the sites of the abdomen and peripheral edema.

The main etiologic factors implied in the appearance of the BCS are chronic myeloproliferative diseases (7, 8), hereditary thrombophilias (Protein C and S deficiency, Factor V Leiden, mutant prothrombin), antiphospholipid syndrome and the oral contraceptives (2). Other rare causes are: paroxysmal nocturnal hemoglobinuria, pregnancy, intestinal inflammatory diseases, aspergillosis.

Adresă de corespondență:

I. Voican, University Emergency Hospital, Bucharest

Chronic myeloproliferative diseases are the main cause of BCS, 10-40% of the cases being represented by Polycythemia Vera (PV).

Thrombotic events are one of the most frequent complications (20-30%) and the main cause of mortality (30%) of PV patients. They appear most frequently in the first years of diagnosis, being one of the initial presenting signs of chronic myeloproliferative diseases. The thrombosis could affect the arteries as well as the veins, and their presence in unusual sites like the portal system or mesenteric system is frequently associated with Polycythemia Vera (6) and Essential Thrombocythemia.

Lately the importance of V617F mutation of JAK2 kinases in the pathogenesis of BCR-ABL negative chronic myeloproliferative diseases was described (4,5), this being correlated with an increased risk of thrombosis in these patients, apart from the patients with idiopathic thrombosis, that do not appear in the context of a chronic myeloproliferative disease. The idea that studying the presence of V617F mutation of JAK2 gene could be used in the diagnosis of a chronic myeloproliferative syndrome accompanying a thrombotic accident was postulated, especially when the thrombosis appear in an unusual place like portal or mesenteric system (3). Among all CMD, the V617F mutation of JAK2 gene was most frequently identified in PV (65-97%).

CASE REPORT

Patient P.I., aged 54, was admitted in the Hematology Department for a rapid volume increase of the abdomen and a diffuse abdominal pain. From the medical history we notice that the patient, smoker and chronic alcohol consumer, have had gum bleeding for a year, progressive physical asthenia and weight loss (10 kg in 2 months).

Physical exam revealed facial plethora, conjunctival hyperemia and scleral jaundice, cyanosis of the nails, "drum stick" fingers, peripheral edema, abdominal collateral circulation, increased abdominal volume through hepato-splenomegaly (liver with prehepatic diameter of 16 cm, increased consistency, painful on palpation, spleen diameter of 17 cm, increased consistency, painful) and ascitis.

Laboratory investigations showed erythrocytosis, thrombocytosis and leukocytosis (Hb = 20g/dl, Ht= 62,6%, WBC = 18.000/mm³ - S 80%, Eo 1%, B 1%, Ly 9%, Mo 9%, Plt = 1.000.000/mm³), hepatocytolysis (AST, ALT=15 x normal

value), cholestasis (GGT= 3 x NV, ALKP= 2 x NV, BR= 3 x NV), all coagulation times spontaneously prolonged (PT= 19,9sec; INR= 1,62; APTT= 41,9sec), hypoalbuminemia (albumin =2,7g/dl) and hypocholesterolemia (cholesterol=120mg/dl).

Regarding this clinical and biological picture, the next investigations were conducted towards the finding of the etiology of hematological and anasarca picture. Bone marrow biopsy reveals hyperplasia of all cell lineages, with increased erythroblast clumps, frequent polymorph, dispersed megakaryocytes, a slight deviation to the left of the white blood cell line with maintained neutrophilic maturation, without clusters of intrasinusal hematopoiesis. The histopathologic exam is highly suggestive for a chronic myeloproliferative syndrome without medullar fibrosis. The peripheral blood cell count showed values of all blood parameters with the predominance of erythrocytosis and thrombocytosis, with slight leukocytosis with normal formula, associated with a normal value of leukocyte alkaline phosphatase (LAP score 23), as well as a decreased value of endogen erythropoietin (Epo 3 mUI/ml), stand up for Polycythemia Vera diagnosis. This was sustained later by finding V617F mutation of JAK2 gene at the PCR exam.

Chronic myeloproliferative diseases frequently associate different grades of hepato-splenomegaly, massive organ enlargement being found especially in the advanced stages of the disease (after years of evolution) or when the disease become complicated. In our case, the patient was symptomatic for only one year and the abdominal manifestations (painful hepatomegaly and ascitis) appeared suddenly in approximately two weeks, suggesting the superposition of an aggravating event. Knowing the increased incidence of venous thrombosis in PV, the suspicion of suprahepatic veins thrombosis (Budd-Chiari syndrome) was raised. The abdominal ultrasound confirmed the clinical suspicion (the liver with prehepatic diameter of 164 mm, irregular echostructure, intrahepatic biliary ducts with normal caliber, spleno-portal axis of 10 mm, the spleen with long diameter of 165 mm and high quantity ascitis). The Doppler venous exam could not visualize the suprahepatic veins; it found only a weak signal in right suprahepatic vein, suggesting thrombosis, extended to the Inferior Vena Cava. This was confirmed by abdominal CT exam (Fig. 1 and 2).

The investigations were completed with superior digestive endoscopy that found out grade III-IV esophageal varices with red spots and erythema of gastric mucosa.

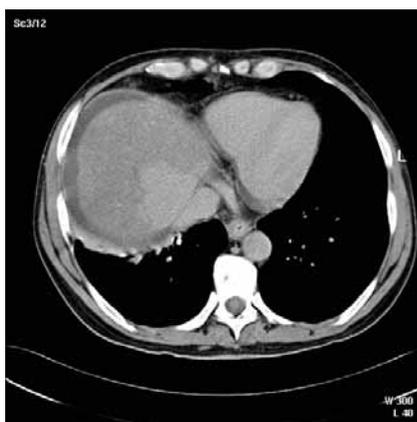


FIGURE 1. Right suprahepatic vein thrombosis extended in IVC



FIGURE 2. Hepatomegaly with caudate lobe hypertrophy and perfusion problems

The clinical picture corroborated with biological data and paraclinical exams raised the suspicion of a alcoholic hepatic cirrhosis (viral serology was negative) vascular and parenchymal failure.

This case raised the following problems of differential diagnosis (Fig. 3):

1. Polycythemia vera complicated with Budd-Chiari syndrome that induced secondary hepatic modifications or

2. Polycythemia Vera associated with hepatic cirrhosis = Mosse syndrome complicated with Budd-Chiari syndrome

For the clarification of this controversy, a hepatic biopsy was necessary – but this was contraindicated at that moment due to the very serious state of the patient, to the hemorrhagic risk known to be associated with chronic myeloproliferative disease and to the urgent need of institution of the anticoagulant treatment. More than that, the debate on this aspect was pure theoretical, because it did not change the treatment, but only the prognosis:

- The hepatic lesions are irreversible in Mosse syndrome
- If the hepatic changes are determined by PV associated with Budd-Chiari syndrome, rapid permeation of SHV could significantly decrease the degree of hepatic affection with subsequent decrease of portal hypertension and functional improvement.

Urgent initiation of complex cytostatic treatment (with Hydroxy-carbamide), anticoagulant (with unfractionated Heparin in continuous administration and later oral anticoagulant), together with serial phlebotomies, assured a rapid favorable evolution with normalization of hematological parameters, disappearance of the phenomenon of hepatic failure and reduction of thrombotic process with partial removal of the obstruction of SHV and complete permeation of IVC.

The patient continuously takes cytostatic and anticoagulant therapy with the maintenance of normal hematological and hepatic parameters, without ascitis, but with persistence of grade I-II esophageal varices.

To conclude, the major thrombotic accident – with an extremely reserved prognosis – associated to a chronic myeloproliferative disease,

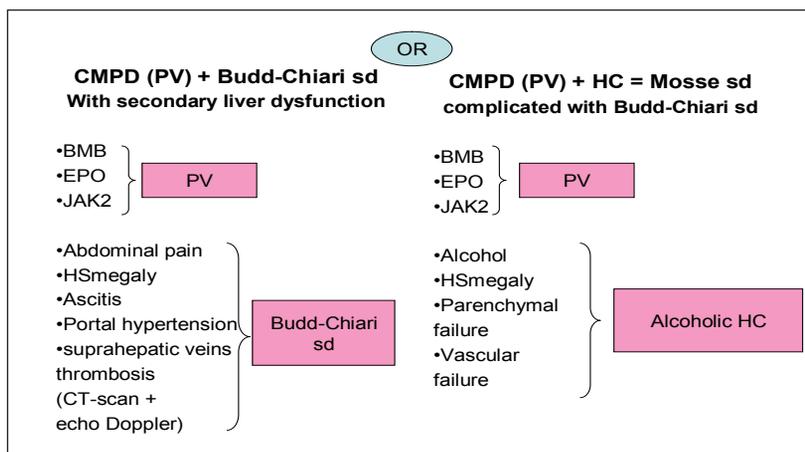


FIGURE 3. Differential diagnosis

justifies an aggressive anticoagulant treatment even in the presence of an increased hemorrhagic risk generated by a chronic liver disease

associated with a deficit in coagulation factors synthesis, high grade esophageal varices and portal gastropathy.

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