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Intrahepatic Portal Hypertension Syndrome Secondary to Primary Myelofibrosis: About A Case

Martial GU[1*], Samah AS[1], Armel Y[1], Adil AE[1], Sofia O[2], Zouhour S[1] and Khadija K[1]

[1]Gastroenterology Department. Mohammed VI University Hospital Center, Marrakech, Morocco

[2]Physiology Laboratory Faculty of Medicine and Pharmacy. Cadi ayyad University, Marrakech, Morocco

***Corresponding author:**

Ulrich Martial Gouton,
Gastroenterology Department. Mohammed VI University Hospital Center, Marrakech, Morocco,
E-mail: emji1806@gmail.com

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1. Summary

In primary myelofibrosis (PM), it is rare to observe PH by intrahepatic block secondary to hepatic myeloid metaplasia. Its diagnosis is histological based on liver biopsy. Splenomegaly and hepatomegaly are the main signs found at the beginning of the disease, while ascites and digestive hemorrhage are complications that cloud the prognosis. The etiological diagnosis of PH was retained by eliminating other causes in our patient in view of the very telling clinical context. Management by diuretics and endoscopic ligation of the varicose veins allowed good control of the complications. Nevertheless, adequate etiological treatment of PD is required, otherwise aggravation of PH and recurrence of PH complications is certain, as in our patient's case.

2. Introduction

Non-cirrhotic intrahepatic portal hypertension (PH) is less frequent but covers a wide range of etiologies. Some of these non-cirrhotic intrahepatic PH are secondary to hepatic or general diseases whose diagnosis can be evoked on the very particular clinical context. The association of portal hypertension and myeloproliferative syndromes has been frequently observed. In most cases, portal hypertension is due to thrombosis of the hepatic, portal or splenic veins, linked to the increased tendency to hypercoagulability of these diseases such as polycythemia or essential thrombocythemia. Portal hypertension is a rare (<10%) initial presentation of PFM, and all the more so when it is without extrahepatic venous involvement [1,2]. In this presentation, we report the case of a patient in whom primary myelofibrosis revealed by intrahepatic portal hypertension.

3. Clinical Case

A 60-year-old woman of low socioeconomic status was hospitalized for abdominal pain. The patient presented with left hypochondrial heaviness associated with early satiety and abdominal distension evolving since 4 years. She had no particular history. The examination revealed a patient in good general condition, a splenomegaly grade 5 with a homogeneous hepatomegaly at 18 cm. She had abdominal collateral venous circulations, with an edemato-ascitic syndrome. Ultrasound coupled with abdominal Doppler showed a homogeneous hepatosplenomegaly with regular contours and without nodules. The portal veins were dilated to 2 cm and the splenic veins were unobstructed and permeable; the suprahepatic veins were normal. The oesophageal fibroscopy revealed grade II esophageal varices. The cardiac function was preserved. The biological workup showed:

- In the ascites fluid: Protein at 16 g/L (SAAG at 32g/L) White blood cells at 85/mm3, in favor of a transudate ascites not superinfected.
- Preserved liver function (TP = 80%, albumin = 43 g/L, total cholesterol = 1.09 g/L, blood glucose = 0.83 g/L, total bilirubin = 7 mg/L, GGT = 54 IU/L, PAL 151 IU/L, ALAT 13 IU/L, ASAT 31 IU/L. LDH = 2239 IU/L
- Blood count + smear: Hb 9.4 g/dL (normocytic normochromic anemia) with anysocytosis and dacryocytosis, platelets = 658000 with numerous signs of dysgranulopoiesis. WBC = 17400 with predominantly neutrophils.
- The blood smear also showed 31% myeloma with 3% circulating blasts.

- Osteomedullary biopsy: morphological appearance of severe myelofibrosis with osteosclerosis, hypoplastic hematopoietic marrow without tumor proliferation.
- Absence of Philadelphia chromosome, JAK 2, and CALR mutation, absence of t (9; 22) and BCR/ABL rearrangement.

Our patient refused to undergo liver biopsies. Given these arguments, the diagnosis of primary myelofibrosis complicated by PH was retained. The patient was treated with methotrexate if ruxolitinib was not available. For the PH syndrome, she benefited from 6 iterative sessions of esophageal varicose vein ligation until their eradication and was put on diuretics (spironolactone 100mg/day and furosemide 40mg/day for 6 weeks) allowing the drying of ascites and edema. Hepatic elasticity evaluated by fibroscan was estimated at 7.3 KPa. After 3 years, the patient was seen in the emergency room for a grade III esophageal varices rupture associated with refractory ascites.

4. Discussion

Primary myelofibrosis (PMF), formerly known as myeloid splenomegaly, is both the rarest and most severe of the Philadelphia-negative myeloproliferative neoplasias (Ph1-). The prevalence of MFP is 0.71/100,000 in Korea and 0.51/100,000 in Europe but 3/100,000 in Norway, with an overall 5-year survival of 55%. The sex ratio is 2 men to 1 woman. PD usually affects people over 50 years of age, with the average age at diagnosis being between 60 and 65 years [3] as found in our case. Functional signs are dominated by manifestations of splenomegaly. Splenomegaly results from myeloid metaplasia of the spleen. In our patient, it was responsible for an abdominal discomfort described in 54% of the patients, due to its impressive volume, and a post-prandial distress syndrome present in 64% of the patients. These sensations are superimposed by acute attacks due to splenic infarction [1]. Hepatomegaly is an inconsistent diagnostic sign present in 50%. This hepatomegaly is histopathologic ally consistent with myeloid metaplasia. Biopsies show a non-cirrhotic liver parenchyma with evidence of extra medullary hematopoiesis of varying degrees and infiltration by granular precursors, erythroblasts and megakaryocytes in the hepatic sinusoids. Portal infiltration is usually much more moderate. The fibrosis of the portal spaces is inconstant, discrete and not annular. The liver functions remain normal for a long time and the liver enzymes are little disturbed. An erythropoietic activity could be demonstrated by studying the incorporation of radio-active iron. It is moderate and generally less marked in the liver than in the spleen [4].

Portal hypertension rarely occurs early (<10%), rather late, in 7% to 17% of cases. In our patient, PH was clinically significant, reflecting the long-standing course of her pathology. PH results in asymptomatic or ruptured esophageal varices, disturbances of the liver balance, and (late) edemato-ascitic syndrome, which considerably darkens the prognosis of PFM. The mechanisms are complex and often interrelated: vascular obstruction and increased blood flow secondary to large splenomegaly accompanied by increased portal flow (active or hyperkinetic PH) are associated. Vascular obstruction causing PH can occur at different levels. The main causes in hematological proliferations are portal and suprahepatic thrombosis (Budd Chiari syndrome) [1]. These were excluded in our case. In the absence of these 2 conditions, 2 theories have been proposed: for some authors, the main contributing factor is probably the drastic increase in blood flow from the enlarged spleen. The second factor is increased intrahepatic resistance due to sinusoidal narrowing and intrahepatic obstruction caused by extramedullary hematopoiesis and infiltration of the liver by myeloid cells [5]. In the absence of signs of cirrhosis and portal or hepatic vein thrombosis, and in view of the large hepatomegaly and splenomegaly, a non-cirrhotic intrahepatic block by extramedullary hematopoiesis causing sinusoidal obstruction associated with portal hyper flow was most likely in our patient.

The management of this PH syndrome and its complications is based on a combination of drug, endoscopic and surgical means as in PH on cirrhosis, including diuretics, ligation and sclerotherapy. The use of elastic ligation and spironolactone for esophageal varices and ascites, respectively, allowed us to obtain good results identical to the authors of cases published in the literature [5,6,7]. TIPS is considered in patients with intrahepatic obstruction of the portal system and when portal, splenic or hepatic vein thrombosis has occurred. Current indications for TIPS are recurrent variceal bleeding and refractory ascites; in failure of drug and endoscopic treatment, both of which could accompany advanced PFM. The therapeutic value of TIPS has not been systematically studied in PFM. Only a few articles have been published regarding the use of TIPS for PH secondary to PFM with myeloid metaplasia, however they report relevant results that confirm the feasibility and efficacy of TIPS in this condition [8-11].

Here splenectomy, long discouraged, seems to regain a certain place. In any case, these are indications that are not universally adopted. The indication is to be discussed in the face of a voluminous and/or symptomatic splenomegaly (39%) (splenic fissure/rupture, splenic infarction), responsible for Http (10.8%), accompanied by severe cytopenias with significant transfusion requirements (45, 3%), thrombocytopenia (4.9%), after failure of medical treatment [1,11].

In the context of PH, an evaluation of the portal and hepatic vascular system by ultrasound coupled with color Doppler, portography with quantification of portal flow are necessary to exclude Budd chiari syndrome or portal or splenic thrombosis (these under other treatments) and ensure the presence of hyperkinetic PH; basis of splenectomy. In the event of a modification of the hepatic architecture on the preoperative biopsies, splenectomy loses its interest [2,6].

After splenectomy PH is reduced in 50 to 70% of cases. It also provides these patients with an undeniable palliative benefit: the symptoms directly related to the large spleen completely disappear, the need for transfusion decreases and the resolution of severe thrombocytopenia [1,11]. In a Mayo Clinic report of 314 splenectomized

patients for primary myelofibrosis, 28% postoperative complications were recorded, including infections, hemorrhage, abdominal venous thrombosis which can be extensive and fatal secondary to loss of sequestration splenic platelets; the postoperative use of heparin could prevent the occurrence of early thrombotic events after splenectomy [2,11,12]. In addition, other specific complications of splenectomy include the aggravation of hepatomegaly due to the accentuation of extramedullary hematopoiesis in the liver in 16%-24% of splenectomized for MFP leading to liver failure in some cases. The major complication concerns acute leukemic transformation [5,11].

5. Conclusion

The mechanism of intrahepatic portal hypertension in patients with MF is still controversial, but is believed to be mainly related to portal hyper flow secondary to enlarged spleen. There is no fundamental difference in the signs and management of its complications compared to other causes of PH. The recommendations on the realization of the TIPS are not consensual and require more experiences. Splenectomy should be performed in emergencies or when other therapeutic alternatives have failed. The complications of splenectomy and the fact that it has not been shown to improve overall survival in patients with MF with myeloid metaplasia, should be strongly considered before proceeding with splenectomy to manage the PH.

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