Splanchnic vein thrombosis as a first manifestation of primary myelofibrosis

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Abstract

Myeloproliferative neoplasms are chronic disorders of clonal hematopoietic stem cells, characterized by an overproduction of functional granulocytes, red blood cells, and/or platelets, and one of the major complications is the occurrence of venous and arterial thrombotic problems caused by increased platelet aggregation and thrombin generation. In this study, 11 cases of primary myelofibrosis (PMF) were evaluated, and two debuted with splanchnic venous thrombosis (SVT); so after seeing the results of this study and of world literature, it is suggested that in patients with SVT, diagnostic methods for PMF like the JAK2V617F mutation should be included.

KEY WORDS: *Myeloproliferative neoplasms. Primary myelofibrosis. Splanchnic vein thrombosis. JAK2V617F mutation.*

Introduction

Myeloproliferative neoplasms (MPN) are chronic disorders of clonal hematopoietic stem cells, characterized by overproduction of functional and mature granulocytes, red blood cells, or platelets[1].

MPNs have an incidence of approximately 2–3 per 100,000 population per year, with a median age at diagnosis being approximately 65 years[2].

Splanchnic vein thrombosis (SVT) exact pathogenic mechanism in MPN remains unsolved; in addition to SVT characteristic erythrosis and thrombocytosis, platelet and leukocyte function abnormalities appear to play a pathogenic role[3]. One of the MPNs main complications is the appearance of venous and arterial thrombotic problems caused by increased platelet aggregation and thrombin generation, which is one of the most common underlying causes of abdominal vein thrombosis[1].

Patients with MPNs, such as polycythemia vera (PV), essential thrombosis (ET), and primary myelofibrosis (PMF), are at higher risk for thrombosis and bleeding with regard to the general population. The prevalence of SVT (Budd Chiari, portal, and mesenteric) in MPN as initial manifestation is 31%, with it being more common in PV and PMF. One-fifth of the patients with PMF will have SVT as initial manifestation[4].

PMF is an MPN that is characterized by progressive fibrosis of the bone marrow and development of extramedullary hematopoiesis. Classically, it evolves by stages, initiating with a proliferative stage and arriving to the characteristic syndrome of progressive anemia with teardrop erythrocytes or dacryocytes, myeloid and erythroid immature elements (leukoerythroblastosis) in peripheral blood, splenomegaly, fatigue, bone pain, night sweats and weight loss, with reduced quality of life and shortened survival. Some patients evolve to leukemic transformation. PMF diagnosis is based on a combination of clinical, morphologic, cytogenetic, and molecular criteria[5]. The criteria for establishing the MPN diagnosis include the appearance of characteristic changes in peripheral blood cells (hemoglobin

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and thrombocytosis increase) and bone marrow findings. However, in patients with SVT, the pertinence of these criteria that are commonly used for MPN diagnosis is controversial, since due to the presence of portal hypertension, which leads to hypersplenism and hemodilution, SVT's characteristic thrombocytosis and erythrocytosis may be masked[6].

In 2005, the JAK2 V617F mutation was identified as the most common molecular anomaly in MPN[7]. Formerly, MPN diagnosis in patients with SVT was based on bone marrow biopsy results and erythrocyte colonies growth in the absence of exogenous erythropoietin, which indicates spontaneous endogenous erythroid colonies. At present, the JAK2V617F gain-of-function mutation that leads to the development of MPN is one of the most important strategies for MPN diagnosis. This mutation is present in nearly all patients with PV and in about 50% of patients with ET and PMF. In portal vein thrombosis, mean MPN and JAK2V617F prevalence have been 31.5% and 27.7%[4], respectively. To obtain a diagnosis in patients with SVT and in individuals with peripheral blood cells normal counts, the presence of MPN should be investigated by assessing for the JAK2V617F mutation, and in patients with negative JAK2V617F mutation, screening for calreticulin mutation should be carried out, and if both are negative, bone marrow histology analysis should be considered.

Another anomaly that should be taken into account both for diagnosis and treatment are esophageal varices and gastrointestinal hemorrhage, which, in spite of being common complications in patients with liver cirrhosis, sometimes are produced in patients with non-cirrhotic portal hypertension that may be due to splenic vein thrombosis, including the portal and mesenteric veins. In MPN, these are risk factors for the development of splenic vein thrombosis[8], which represents an additional risk for having a life-threatening hemorrhage[9].

The association between the JAK2 mutation, esophageal varices and portal vein thrombosis translates into direct clinical consequences for patients, and the main purpose is, therefore, preventing variceal hemorrhage and early stopping MPNs[10]. Arterial and venous thromboembolism substantially contributes to morbidity and mortality of patients with MPN, since they cause approximately 45% of all fatal events. SVT safe and efficacious prophylaxis remains the main obstacle in the management of patients with MPN. One general recommendation is that, in patients with MPN, after a SVT major event, short-term therapeutic anticoagulation, that is, from 3 to 6 months, should be implemented. Thereafter, similar to recommendations for idiopathic deep thrombosis, individual risk for venous thrombosis relapse should always be evaluated weighing the risk of hemorrhage[9]. In three retrospective studies of cohorts of non-cirrhotic patients with SVT, long-term anticoagulation was associated with lower risk for recurrent thrombosis[8]. Overlapping with anticoagulant therapy of at least 3 months duration should be with Vitamin K-antagonists or direct oral anticoagulants (such as rivaroxaban, which was used in this study's cases)[11]. Treatment of the underlying prothrombotic cause, in this case, MPN, should be concomitantly started. As a matter of fact, in a retrospective cohort study, the benefits of early treatment were observed in underlying myeloproliferative disorders[12]. Ruxolitinib (also known as INC424 or INCB18424) is an oral, potent and selective JAK1 and JAK2 inhibitor that is approved for the treatment of PMF[13]. Continuous oral therapy with ruxolitinib can reduce splenomegaly and improve quality of life in patients with MF[14]. On the other hand, ruxolitinib was associated with higher frequency of anemia and thrombocytopenia, results that are consistent with those of several previous studies[15,16]. Ruxolitinib has also been shown to be able to cause serious side effects, such as infections, and control with complete blood count is, therefore, recommended. Most common adverse reactions in PMF (> 10%) are urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, dizziness, headache, alanin aminotransferase and aspartate aminotransferase elevation, hematomas, and weight gain. Common adverse reactions in PMF (1–10%) are herpes zoster infection and flatulence. Infrequent adverse reactions in PMF include tuberculosis[17]. However, follow-up is still necessary to assess long-term results with regard to ruxolitinib efficacy and safety[14].

PMF is the MPN with the worst prognosis, with life expectancy estimated at 5–7 years, and exceeding 10 years in younger patients with favorable prognostic factors. It is important for the prognosis of each patient to be identified to guide therapeutic decision-making. Some variables to be considered when assessing the prognosis include age, constitutional symptoms (night sweats, fever, and significant weight loss), hemoglobin, white blood cell count, peripheral blood blasts, platelet count, red blood cell transfusion requirements, and unfavorable karyotype[18].

Presentation of Cases

Eleven patients with PMF were studied at Laboratorios Fátima de Michoacán, out of which two had SVT as the initial manifestation.

Case 1

Case 1 is a 66-year-old female with weight loss and abdominal pain. SVT (portal and superior mesenteric vein), ascites and hepatosplenomegaly were detected, with findings of Grade V esophageal varices on esophagogastroduodenoscopy. JAK 2-positive MF was diagnosed, with intermediate DIPSS Plus Score. She was treated with ruxolitinib and rivaroxaban since her diagnosis. In the control follow-up, hematemesis was detected with no hemodynamic repercussion and no need for transfusion. Esophagogastroduodenoscopy showed a gastroesophageal junction ulcer with signs of bleeding and fibrin clot, as well as Grade II esophageal varices. In subsequent controls, no adverse effects have been so far detected.

Case 2

This case is a 57-year-old male with hematemesis. SVT was detected (portal vein, with ascites and hepatosplenomegaly). Grade V esophageal varices with signs of recent bleeding were observed by endoscopy. He was diagnosed with JAK-2-positive MF with intermediate DIPSS Plus Score. As in case 1, he received treatment with ruxolitinib and rivaroxaban, with no complications reported so far.

Discussion and conclusions

In this single-center two-case study, 18.1% of patients with PMF were observed to have SVT as initial manifestation, while reports in the world literature indicate that SVT prevalence in MPN as an initial manifestation is 31% and that it is more common in PV and PMF. Taking into account the results of this study's cases and of the world literature, it is suggested that, when assessing and studying patients with SVT, diagnostic methods for MPN should be included, such as the JAK2V617F mutation detection. Similarly, attention should be paid to the treatment, since if patients with MPN show symptoms of SVT, should be started on anticoagulation therapy for at least 3 months, as indicated by the literature, and be complemented with the necessary measures, including Vitamin K analogs or oral direct anticoagulants, or both, always taking each patient's monitoring and control into account, with risks for hemorrhage and platelet counts being assessed. Furthermore, as shown in the cases, adding a JAK2 mutation inhibitor such as ruxolitinib is possible, but the literature clearly assessing this drug's side effects is scarce, and it is important to consider that those that have been demonstrated include a decrease in blood cells, and it is, therefore, advisable to maintain hematological surveillance and carry out a subsequent assessment to observe long-term effects. Patient prognosis varies according to different criteria, such as the age, symptoms, anomalies found in the blood count and karyotype, with survival prognosis being approximately 5–7 years, which makes it important for opportune diagnosis to be established and for attention to each individual's characteristics to be paid, as well as maintaining a treatment focused on preventing complications and improving quality of life.

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