Case study

Polycythemia Vera with Budd-Chiari Syndrome Associated: A Case Report

ABSTRACT

The Polycythemia Vera (PV) is a disease characterized by a myeloproliferative disorder with an increased production predominantly the erythroid lineage and your main clinical condition stems from prothrombotic phenomena. Budd-Chiari Syndrome (BCS) is related to an obstruction of the hepatic venous flow leading to occlusion of hepatic veins and their tributaries. Genetic and environmental factors can interact for risk determination of venous thromboembolism. The risk associated with SNP 677C>T and 1298A>C of the methylenetetrahydrofolate reductase (MTHFR), 1691G>A of the Factor V Leiden (FVL) and 20210G>A of the prothrombin (FII) genes were investigated in many studies involving thrombosis. This case report describes the clinical, hematological and biochemistry data about a 48-year-old woman diagnosed with PV and a BCS associated, also carrier of 677C>T SNP in homozygosity. The patient started therapy with phlebotomy, hydroxyurea and oral anticoagulant. Currently, she presents a better clinical and laboratory condition with normalized values of hematological and platelet indices. This case report aims to contribute with evidence of related comorbidities and makes it possible to report that genetic factors are involved, since the patient's mother had already been diagnosed with PV in 2016 at 78 years old. For this main result, we understand that it is clear that a family genetic study can reveal clinical modifying factors in these patients, as there are different clinical severities in the family. Furthermore, we believe in the need for a greater number of randomized clinical trials to add better evidence to complement an ideal therapeutic approach in these patients.

Keywords: Myeloproliferative disorder, Chiari Syndrome, thrombosis, genetic disease, polymorphism.

INTRODUCTION

Polycythemia Vera (PV) is a chronic clonal myeloproliferative neoplasm characterized by an increase in the hematopoietic lineage, mainly erythrocytes, leukocytes and platelets [1]. The alteration mainly in erythropoiesis promotes an increase in blood viscosity, stimulating a pro-thrombotic state, in addition to an increase in cardiovascular risks and a substantial load of symptoms that include itching, fatigue and night sweats [2].

The prevalence of PV is slightly higher in men and usually occurs in individuals over 50 years old. Studies show that less than 1% have the disease before 25 years. According to Tefferi et al. (2013) [3], the presence of the mutation in JAK2 gene occurs in 98% of patients, the increase in erythrocyte mass in 91% and mean hemoglobin levels greater than 18.5 g/dl in men

and greater than 16.5 g/dl in women were the main findings in patients diagnosed with Polycythemia Vera [4].

Budd-Chiari Syndrome (BCS) is characterized as an obstruction of the hepatic venous flow involving the occlusion of the inferior vena cava or of the hepatic veins and their tributaries. This obstruction is commonly related to trauma, coagulopathies, sickle cell anemia, leukemia, Polycythemia Vera and liver abscesses [5]. Clinical manifestations in BCS are distinct and include ascites, hepatomegaly and abdominal pain in the subacute form of the disease, often with non-specific laboratory alterations such as mild elevation of transaminase levels [6].

Prothrombotic factors are present in most patients diagnosed with BCS. The literature demonstrates a fundamental role of thrombophilic genetic factors in the occurrence of thrombosis [7]. The prevalence of these depends in part on geographic and genetic differences between patients. In this case report, we investigated four SNPs in three genes with important functions related to thrombosis.

CLINICAL CASE

Female patient, 40 years old, with a family history of Polycythemia Vera (mother and sister). In January 2016, she was admitted to a hemotherapy center in the northern region of Brazil due to dehydration and hemoconcentration, with laboratory results showing erythrocytosis, high hemoglobin levels and high percentage of hematocrit. She had no skin changes throughout the body or neurological changes, however, showed intense hepatomegaly and high levels to Aspartate transaminase (66.0 U/L) and Gamma glutamyl transpeptidase (168.0 U/L), while low level to Total Proteins (1.6 g/dl). The virology was negative to HIV, B and C Hepatitis Virus. Ultrasonography (USG) of the upper abdomen showed renal microlithiasis and hydronephrosis in the right kidney, ascites, calcifications in the intervertebral spaces of the spine and echogenic image in the right hepatic lobe.

In February (2016), the endoscopic examination showed intense pangastritis with erosions in the antrum, antral deformity and no visualization of varicose cords. Biopsy revealed duodenitis with duodenal bulb deformity. Computed Tomography showed the results described below:

– Accentuated narrowing without flow in the intrahepatic segment of the inferior vena cava;
– Hepatic veins filled;
– Exuberant perihepatic, perisplenic and mesenteric collateral circulation, with signs of cavernous transformation of the portal vein;
– Increased caliber in the immediately infrahepatic segment of the inferior vena cava and renal veins;
– Liver with increased dimensions and lobulated contours, with signs of hypertrophy of its central region to the detriment of the peripheral one, with signs of hypertrophy of the caudate lobe;
– Predominantly peripheral heterogeneous enhancement pattern of the liver parenchyma, with enhancement of associated curvilinear structures;
– Sparse hipervasculares nodules in the liver parenchyma, with the largest in segment VII, measuring 0.9 cm, corresponding to regeneration nodules;

– Largely enlarged spleen's dimensions, showing areas without impregnation by contrast medium in its parenchyma, the largest of which is lower-posterior to the left, measuring approximately 9.6 cm;
– Gallbladder not identified in its usual topography;
– Pancreas with anatomical features;
– Normal caliber ureters;
– Normal Adrenal Glands;
– Umbilical hernia, where it insinuates into the adipose tissue, mesenteric vessels and intestinal segment.

Yet in February 2016, magnetic resonance of the upper abdomen validated the same findings from the Computed Tomography, confirming the diagnosis of Budd-Chiari Syndrome, in addition to the presence of Splenomegaly with splenic infarcts. In August 2016, a High-resolution two-dimensional ultrasonography (HR-USG) of the Upper Abdomen detailed parenchymal liver disease, reduced-caliber of the hepatic vein and portal vein, splenomegaly and cholecystectomy. In August 2017, a new HR-USG of the Upper Abdomen was performed with Doppler, detecting chronic liver disease with portosystemic collateral circulation; portal vein thrombosis with cavernomatous transformation; splenomegaly; ascites and tapered hepatic and cava veins in some segments. Upper gastrointestinal (UGI) endoscopy the 2017 to 2020 years revealed esophageal varices, gastric varices, mild portal hypertensive gastropathy and duodenal subepithelial lesion (Figure 1).

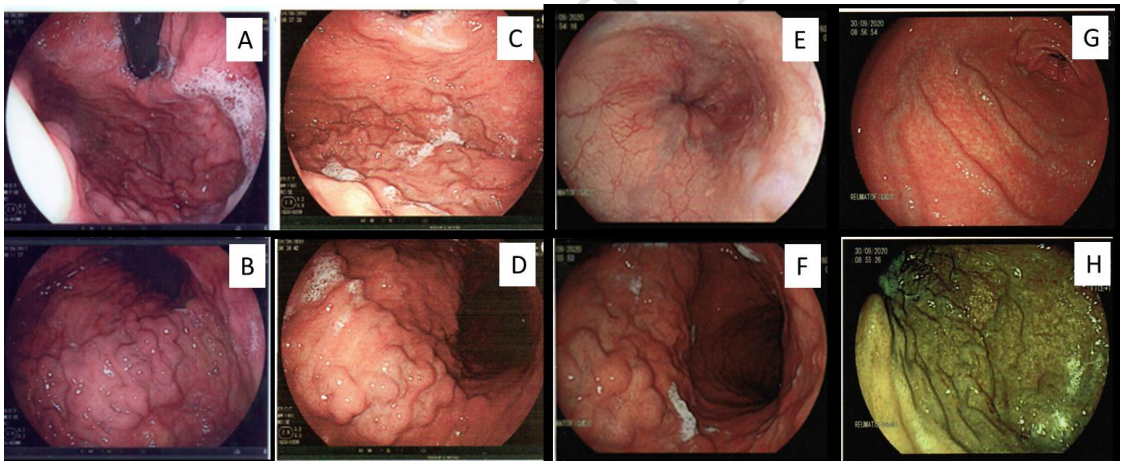

Figure 1: Upper gastrointestinal (UGI) endoscopy showed esophageal and gastric varices.
A-B: UGI in 2017 / C-D: UGI in 2018 / E-F: UGI in 2019 / G-H: UGI in 2020.

A bone marrow biopsy was performed in March 2017, revealing hyperplastic granulocytic with typical mature forms, hyperplastic erythrocytes with hyperchromatic forms and accentuated hyperplastic megakaryocytes with large hyperlobed forms. The biopsy also clarified the presence of a sparse reticulin network, with intersections, especially in the perivascular areas, absence of iron deposits, perivascular collagen deposits and distinct paratrabecular zone, concluding that it was bone marrow panmyelosis suggestive of Polycythemia Vera. With the findings of the exams performed, the patient was then diagnosed with Polycythemia Vera associated with Budd-Chiari Syndrome.

Noteworthy, in March 2016, the patient had started treatment with 0.4 ml enoxaparin sodium 40 mg subcutaneously for 10 days with normal prothrombin time (PT). Then warfarin

sodium 5 mg orally once a day was indicated for treatment. In September 2016, the patient started treatment with bleeding once a month to remove 300 mL of total blood during September 05th and December 20th 2016. In June 2017, due to the non-effective response to treatment, the patient started using hydroxyurea (HU) 500 mg daily during two months (12/12 hours), normalizing the erythrocytes, hemoglobin, hematocrit, and platelets parameters. Thus, treatment with Hydroxyurea 500 mg was reduced to one capsule a day and warfarin sodium 5 mg orally once a day.

The molecular assay for thrombophilic factors to risk of thrombosis revealed homozygous for MTHFR 677C>T and wild type to MTHFR 1298A>C, FVL 1691G>A and FII 20210G>A. Her clinical condition remained stable throughout the hospitalization. At discharge, the complete blood count was as follows: RBC 4.38 x106 mm³, Hgb 11.9 g/dL, Hct 35.5%, platelets 154,000/µL, and WBC 4,930/µL. Table 1 shows the hematological data since January 2016 to August 2017.

Table 1 – Hematological parameters data during the follow-up period of treatment

. Hematological data	INITIAL 01/2016	FOLLOW-UP				REFERENCE VALUES
		03/2016	01/2017	05/2017	08/2017	
RBC (10^6/mm³)	6.7 ↑	6.3 ↑	6.36 ↑	8.09	4.38	3.9 to 5,1
Hemoglobin (g/dl)	20.3 ↑	18.1 ↑	14.1	15.8	11.9	11.5 to 14.9
Hematocrit (%)	61 ↑	56.6 ↑	46.6	51.4	35.5	35.3 to 46.1
MCV (fL)	91	89.8	73.3	63.5	81.1	81.0 to 100.2
MHC (pg)	30.3	28.7	22.2	19.5	27.2	26.3 to 32.4
MCHC (g/dl)	33.3	32	30.3	30.7	33.5	30.5 to 34.3
RDW (%)	20.2 ↑	16 ↑	16.5 ↑	18.1 ↑	33.8 ↑	11.9 to 15.5
Reticulocytes (%)	2.58	1.12	1.29	1.31	1.46	0.5 to 2.0
Leukocytes (x10^9/L)	15.900 ↑	14.250 ↑	10.970	17.560 ↑	4.930	4.1 to 10.04
Platelets (x10^9/L)	495.05↑	524.12 ↑	645.46 ↑	730.13 ↑	154.09	150.00 to 450.00
ESR (mm/h)	4	12	-	2	42	Up to 20 mm/1ªh
Blood smear 01-2016	Leukocytosis, erythrocytosis and neutrophilia					
Blood smear 03/2016	Normocytic normochromic, rare microcytes and rare macrocytes. Moderate plateletosis					
Blood smear 01/2017	Normocytic normochromic, rare microcytes and rare codocytes. Moderate plateletosis					
Blood smear 05/2017	Mild hypochromia, 1+ Microcytes, rare macrocytes and marked plateletosis					
Blood smear 08/2017	Mild hypochromia. 1+ Microcytes, 2+ Macrocytes and some elliptocytes.					

RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red blood cell distribution width; MPV: Mean platelet volume; SD: Standard Deviation; ESR – Erythrocyte sedimentation rate. ↑: Considerably above the reference value.
Reference Values (Adapted by Rosenfeld et al, 2019) [8]

DISCUSSION

In the case presented the patient sought the health service for showing signs of tiredness, fatigue, intermittent headache, fainting and intense facial flushing, in addition to evident hepatomegaly. The blood count showed an increase in erythrocytes, hematocrit and platelets, confirming the diagnosis of Polycythemia Vera was confirmed by bone marrow biopsy.

Currently, the diagnosis of Polycythemia Vera is performed according to the criteria of the World Health Organization (WHO) [9] and based on a clinical and laboratory evaluation [16]. The WHO suggests that for some cases where the diagnosis of Polycythemia Vera is difficult, additional tests should be performed including peripheral blood smears, erythropoietin levels or endogenous erythroid colony formation in vitro [10]. The tyrosine kinase mutation (JAK2V617F) is highly sensitive (97%) and specific (100%) to distinguish Polycythemia Vera from other causes of increased hematocrit [11]. Unfortunately, this exam was not performed on the patient.

Among the main complications of Polycythemia Vera, thrombosis stands out, being one of the main characteristics for detecting or suspecting the disease, with an incidence of about 20% in patients. In many cases, the disease is accidentally discovered on hemogram, when high values of hemoglobin and hematocrit are presented. Patients have different symptoms, such as headache, dizziness, ischemic accidents, visual changes, pruritus, systolic hypertension and splenomegaly [12].

Clinically, the patient in question had hepatomegaly and splenomegaly and, therefore, the physician requested an Ultrasonography of the Upper Abdomen to investigate the case. The exam detected signs of Budd-Chiari Syndrome, large splenomegaly with infarctions and portal vein thrombosis also evidenced in the magnetic resonance and computed tomography performed.

A large European multicenter study revealed that prothrombotic factors were present in 84% of patients diagnosed with BCS. In patients with BCS, the prevalence of Myeloproliferative Neoplasms, such as Polycythemia Vera, and JAK2V617F mutation was 40.9% and 41.1%, respectively [13].

The clinical presentation of Budd-Chiari Syndrome is heterogeneous and varies from the absence of symptoms to fulminant liver failure. In a multicenter prospective cohort study of patients diagnosed with BCS, ascites was present in 83% of patients, hepatomegaly in 67%, abdominal pain in 61%, esophageal varices in 58% and gastrointestinal bleeding in 5% [14]. The cytoreductive therapy chosen was the use of Hydroxyurea in association with phlebotomy (bleeding) in low doses of oral anticoagulant. This treatment regimen is recommended by experts as a first choice of cytoreductive therapy for patients at high risk of developing the disease. The recommendations for the management of Polycythemia Vera are based on the risk of thrombosis and on a limited number of randomized clinical trials, in addition to observational studies. Therefore, clinical experience still plays an important role in guiding therapy. Study-based guidelines are to keep the hematocrit below 45% and the platelet count below 400,000/mm^3 [15]. In a study that re-evaluated the benefit-risk of using Hydroxyurea in patients with Polycythemia Vera, it showed a reduction in the rate of transformation to myelofibrosis without increasing the risk of leukemia with the use of Hydroxyurea compared to the use of phlebotomy alone. In this study, 1,042 patients were selected and received during follow-up only phlebotomy or hydroxyurea to maintain hematocrit levels below 45% [16].

The use of HU in our patient resulted in clinical and laboratory improvement. According to WHO, the risk of leukemic transformation and fibrotic progression is less than 5% and 10% in

10 years respectively. Therefore, the advance in the case of Polycythemia Vera in the case in question depends mainly on the risk of thrombosis and less probability of the possibility of the disease progressing to acute leukemia or myelofibrosis with myeloid metaplasia [17].

Our patient showed MTHFR 677C>T mutation. Although this mutation is relatively common in our population with 8% to 43% of Caucasian Brazilians carrying a 677C>T polymorphisms. the thrombotic risk to homozygous individuals is significant [18,19]. Some factors like dehydration, high blood pressure, high cholesterol, lack of activity and obesity are known risk factors for thrombosis and could raises the incidence in PV patients [20]. In our patient showed the MTHFR 677C>T homozygous, polycythemia, platelet aggregation and thrombocytosis may increase the risk for thrombotic complications. The interaction between PV and MTHFR 677TT warrants further study to try to explain risks associated with simultaneous prothrombotic gene mutations and to ascertain treatment in patients with these mutations.

CONCLUSION

The reported case contributed as further evidence of Polycythemia Vera, in addition to Budd-Chiari Syndrome resulting from the evolution of the pro-thrombotic effects of Polycythemia Vera. Despite reporting clinical and laboratory improvement, the patient must continue with follow-up to control complications arising from the evolution of the disease that may occur, such as leukemia and thrombosis.

The inheritance of the disease between the patient and the mother is questioned, as it is a rare disease and the patient is a 48-year-old young adult, as well as the need for a greater number of clinical studies to evaluate the treatment of diseases reported to guide treatment approaches.

CONSENT AND ETHICAL APPROVAL

The study was approved by two Research Ethics Committee (CEP) at the Federal University of Amazonas (UFAM) under the CAAE number 83413718.6.3001.5020

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