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A Case of Budd-Chiari Syndrome Associated with Erythrocytosis and Homozygous MTHFR C677T Mutation

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Authors' contributions

This work was carried out in collaboration among all authors. Author LBS performed the collection of blood samples, the practical and laboratorial parts of the entire project and the molecular tests for the polymorphism genotyping. Author DFA assisted in the collection of samples and digitization of results in data analysis programs. Author JPMN conceived the study and idealized of the project. He helped supervise the project and interpretation of data and drafting the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

An erythrocytosis describes an increased erythrocyte, subclassified into relative due to hemoconcentration or absolute by an increase in erythrocyte mass, defined as an increase in hemoglobin concentration and/or hematocrit in the peripheral blood above the sex-specific normal range. 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

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(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 carrying 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 absolute erythrocytosis 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.

1. INTRODUCTION

Polycythemia, also called erythrocytosis, is caused by the increase in red blood cell mass (Hematocrit), or a decrease in plasma volume, normally accompanied or not with hemoglobin level elevated in peripheral blood [1]. This absolute erythrocytosis can promote an increase in blood viscosity, stimulating a pro-thrombotic state, cardiovascular risks and a substantial load of symptoms that include fatigue and night sweats [2]. Absolute erythrocytosis can be primary as results, for example, from myeloproliferative neoplasms or secondary origin by hypoxia cases or the presence of an erythropoietin-producing tumour. The most common cause of acquired primary erythrocytosis is polycythemia vera (PV), slightly higher in men and usually occurs in individuals over 50 years old [3]. Studies show that less than 1% have the disease before 25 years. According to Tefferi et al. (2013) [4], the presence of the mutation in the JAK2 gene occurring 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 PV [5].

Budd-Chiari Syndrome (BCS) is characterized as an obstruction of the hepatic venous flow involving the occlusion of the inferior vena cava or the hepatic veins and their tributaries. This obstruction is commonly related to trauma, coagulopathies, sickle cell anaemia, leukaemia, Polycythemia Vera and liver abscesses [6]. 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 [7].

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 [8]. 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.

2. CLINICAL CASE

Female patient, 40 years old, with a family history of absolute erythrocytosis (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 hematocrit. Had no skin or neurological changes, however, showed intense hepatomegaly and high levels of 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 and computed tomography showed numerous altered results. The main findings are described next: Accentuated narrowing without flow in the intrahepatic segment of the inferior vena cava;

Exuberant perihepatic, perisplenic and mesenteric collateral circulation, with signs of cavernous transformation of the portal vein; 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 an enhancement of associated curvilinear structures; Sparse hypervascular 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.

Yet in February 2016, the 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-calibre 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 (Fig. 1).

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 PV. Unfortunately, we did not confirm the JAK2 mutation in the patient, and thus, with the findings of the exams performed, the patient was then diagnosed with absolute erythropoiesis 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 for 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.

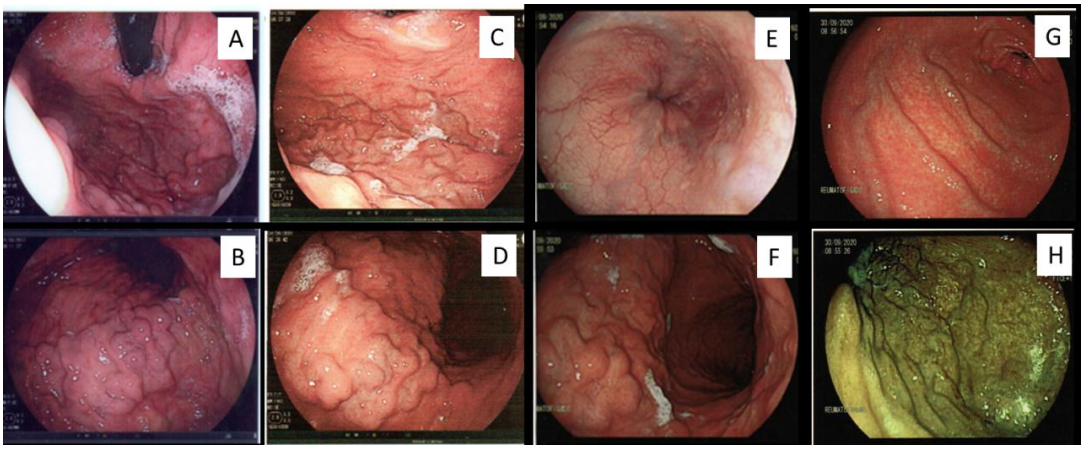

Fig. 1. Upper gastrointestinal (UGI) endoscopy showed esophageal and gastric varices. A-B: UGI in 2017 / C-D: UGI in 2018 / E-F: UGI in 2019 / G-H: UGI in 2020

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

Hematological data	Initial	Follow-up				Reference values
	01/2016	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) [9]

The molecular assay for thrombophilic factors to the 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 from January 2016 to August 2017.

3. 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 absolute erythrocytosis was confirmed by bone marrow biopsy.

Currently, the diagnosis of PV is performed according to the criteria of the World Health Organization (WHO) and based on a clinical and laboratory evaluation. The WHO suggests that for some cases where the diagnosis of PV 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 PV from other causes of increased hematocrit [11]. Unfortunately, this molecular exam was not performed on the patient.

Among the main complications of PV, 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 the primary choice of cytoreductive therapy for patients at high risk of developing the disease. The recommendations for the management of PV are based on the risk of thrombosis and on a limited number of randomized clinical trials, in addition to observational studies. Therefore, the 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/mm³ [15]. A study that re-evaluated the benefit-risk of using Hydroxyurea in patients with Polycythemia Vera, showed a reduction in the rate of transformation to myelofibrosis without increasing the risk of leukaemia 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 patients 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].

Although our patient showed the MTHFR 677C>T homozygous mutation and the thrombotic risk to homozygous individuals are significant this mutation is relatively common in our population, affecting 8% to 43% of Caucasian Brazilians [18,19]. Some factors like dehydration, high blood pressure, high cholesterol, lack of activity and obesity are known risk factors for thrombosis and could raise the incidence in PV patients [20]. In our patient showed the MTHFR 677C>T homozygous, absolute erythrocytosis, platelet aggregation and thrombocytosis may increase the risk for thrombotic complications. The interaction between this clinical state 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.

4. CONCLUSION

The reported case contributed as further evidence of possible PV case, in addition to Budd-Chiari Syndrome resulting from the evolution of the pro-thrombotic effects of absolute erythrocytosis. 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.

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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

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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