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Case Report

Case Report: Paroxysmal Nocturnal Hemoglobinuria (PHN): A Rare Cause of Budd Chiari Syndrome (BCS)

M. Bouissehak[1*], M. Kadiri[1], M. Borahma[1], F. Chabib[1], C. Berhili[1], N. Lagdali[1], I. Benelbardhadi[1], Fz. Ajana[1]

[1]Ibn Sina Hospital- University Mohamed V

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***Corresponding author:** M. Bouissehak
Ibn Sina Hospital- University Mohamed V

Abstract

This is the case of a female patient aged 42, admitted for abdominal distension and abdominal pain, in whom clinical examination revealed a dysmorphic liver with signs of portal hypertension. Abdominal ultrasound coupled with Doppler showed SBC, which was confirmed by abdominal angioscan. A complete etiological workup was performed, which revealed the presence of an HPN clone on flow cytometry. The patient was put on anticoagulation in addition to treatment of the complication of PH, with a good clinical evolution. At present, the patient is still under regular consultation.

Keywords: Budd chiari syndrome – Paroxysmal nocturnal hemoglobinuria - thrombosis.

INTRODUCTION

PNH is a rare acquired clonal disorder of hematopoiesis, characterized by intravascular hemolysis, peripheral blood cytopenias, and thrombosis. PNH clone arises from a hematopoietic stem cell suffering an inactivating phosphatidylinositol N-acetylglucosaminyltransferase subunit A (PIG-A) gene mutation.

Thrombosis, especially in the venous circulation, has been classically recognized as a frequent complication, and the first cause of death, in PNH. The high prevalence of hepatic vein thrombosis in this setting, and its contribution as the most frequent cause of thrombotic mortality has been described in historical

We present the case of a patient who was hospitalized with BCS due to HPN

CASE REPORT

This is the case of a 42-year-old female patient with no hepatic risk factors who was admitted for abdominal distension.

The history of the disease dates back to 6 months before admission to the hospital, with the onset of progressive, homogeneous abdominal distension, gastritis-like epigastric pain and generalized skin pruritus, with no notion of jaundice or externalized digestive hemorragia.

Clinical examination revealed a dysmorphic liver with cirrhotic appearance and signs of portal hypertension (ascites - splenomegaly and collateral venous circulation).

On imaging, abdominal ultrasound coupled with Doppler showed homogeneous hepatomegaly, 02 non-visible hepatic veins (right and left) and signs of portal hypertension (PH).

Abdominal angioscan confirmed SBC at PH stage, with bi-lobular hepatic formations suggestive of pseudonodules associated with SBC.

Liver MRI reconfirmed the diagnosis, without the presence of focal lesions (hepatocellular carcinoma or focal nodular hyperplasia).

Biologically, we had biological cholestasis with gamma-glutamyl transferase (GGT) at 180IU/L with a normal of 44IU/L with a normal value of 44IU/L and Alkaline phosphatases (PAL) at 176IU/L with a normal value of 150IU/L with a normal value of 150IU/L, for which the etiological investigation was negative.

There was no anemia, hemolysis, hepatocellular insufficiency or cytolysis. The Alpha-fetoprotein AFP was negative

The table above show the baseline characteristics of BCS patients with PNH of our case:

Table 1: Baseline Characteristics of BCS Patients with PNH

Baseline characteristics of BCS patients with PNH	Results
Age	42
Gender	Female
Type of outflow obstruction	hepatic veins (right and left
mean symptom	Abdominal distension
clinical examination	Hepatomegaly
SIGNs OF PHT	Ascite, splenomegaly
aspartate aminotransferase	30IU/L
alanine aminotransferase	25IU/L
GGT	180IU/L
PAL	176IU/L
AFP	6,02ng/ML
HB(hemoglobin)	14,5g/dl
PLT(platelets)	133.000/mm³
leucocytes	6010
total billirubin	8mg/L
creatinine	13mg/dl

In the etiological research of the prothrombotic factor, flow cytometry had shown the presence of an erythrocytic HPN clone at 7.4% and granular at 6.1%.

Therapeutically, the patient received non selective beta-blocker (NSBB) treatment for PH, after eliminating all the contraindications, ascites was treated with diuretics and a low-sodium diet with good clinical evolution.

A direct oral anticoagulant (DAC) was initiated, type Rivaroxaban 20mg/day without recanalization of the hepatic veins on follow-up imaging.

Unfortunately, due to lack of resources, we were unable to treat the patient for HPN but the patient's progress has been good and she continues to receive regular follow-up consultations.

The following table summarizes the clinical, morphological and biological characteristics of our case

The table above summarizes the prognostic scores of our case:

Table 2: Prognostic Scores of Our Case

Pronostic score of our case	Results
Rotterdam score	Classe II (1,3)
Clichy score	4,78
MELD score	25

DISCUSSION

INTRODUCTION [1, 2]

PNH is an exceedingly rare acquired disorder of haematopoietic stem cells. Its main clinical features are intravascular haemolysis, anaemia or pancytopenia and a tendency to venous thrombosis, principally of the abdominal and cerebral veins Budd–Chiari syndrome (BCS) is a frequent thrombotic complication classically found in Western series of patients with paroxysmal nocturnal hemoglobinuria (PNH), with a high morbidity and mortality.

Up to 50% of patients with PNH may develop BCS, which is currently the main cause of death in this disorder [. On the other hand, PNH is recognized in 9-19% of tested BCS patients. Therefore, PNH, although extremely rare, is among the main causes of BCS. Current therapies for PNH may achieve a good control of the disease. Hence, the presence of PNH should be considered in any patient with BCS, irrespective of the presence of its distinctive clinical features.

Epidemiology

Prevalence of BCS in PNH Patients[3, 4]

Most data of BCS prevalence in PNH patients come from retrospective series.

Despite their heterogeneity, they show marked differences between the Western and Eastern series (as shown in Tables 7.1 and 7.2), paralleling what happens with thrombosis in PNH.

Western patients show high rates of hepatic vein thrombosis. Asian PNH patients show instead a much lower compromise of hepatic veins, as it occurs with venous thrombosis.

Table 3: The Prevalence of BCS in PNH Patients

Western series		Asian series	
Ziakas	147/465	Lee	7[a]/81
Hall	13/39	Ge	0/10
Kelly	12/34		
Total	172/538 (32%)	Total	7[a]/91 (7.7%)

Prevalence of PNH in BCS Patients [5, 6]

A review of published series shows a highly dissimilar PNH prevalence in BCS patients in different countries. In Western patients, PNH was found as an underlying condition for BCS in 9–19.5% of tested patients. Asian series show a much lower prevalence of PNH, in the range of 0 (in 3 series) to 0.8% of BCS patients, generating doubts about the indication to test for PNH in all BCS patients in those countries.

Table 4: The Prevalence of PNH in BCS Patients

European series	PNH prevalence	Asian series	PNH prevalence
Smalberg	9%	Qi	0.8%
García-Pagan	10.5%[a]	Cheng	0%
Hoekstra	19.5%[a]	Baloda	0%
		Ahluwalia	0%
Total number of PNH/BCS patients	30/223		1/300

Enteric Microbiota in BCS and PNH [7, 8]

The diseases of the liver have been associated with changes in the amount and proportion of the gut microbiota. These changes can cause intestinal mucosa inflammation with bacterial products translocation and subsequent hepatic injury and

Inflammation

Different liver diseases have been associated with changes in the composition of the intestinal microbiota, including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and cirrhosis.

It is possible that these changes could cause inflammatory stimuli in the hepatic circulation, favoring local thrombosis due to complement activation plus the presence of a complement sensitive liver endothelium in PNH patients

Diagnostic [9]

As PNH is a rare disease, and in Asian patients with BCS it is found very uncommonly, a valid question is: peripheral blood flow cytometry to detect a PNH clone must be performed in all patients, or only a subgroup should be screened?

With available data of Western BCS series showing a prevalence of ≥9%, it seems clear that every patient should be studied for PNH. However, in case of Asian patients, flow cytometry to find a GPI negative clone probably should be done to those patients with BCS plus another clinical finding that may increase the probability to have PNH, such as either:

1) Any evidence of hemolysis like high reticulocyte counts, low haptoglobin levels, high LDH levels, high plasma free hemoglobin levels, hemosiderinuria, hemoglobinuria, or
2) Bone marrow failure as marked cytopenias, greater than expected due to hypersplenism, or
3) Thrombosis in other sites (like other splanchnic veins, or another venous or even arterial thrombosis), or
4) The finding at a magnetic resonance imaging (MRI) study of a diffusely reduced
5) signal intensity in the kidney cortex in a patient with BCS, suggestive of hemosiderosis, rising the clinical suspicion of PNH

Certainty Diagnosis [10, 11]

PNH diagnostic tests have improved considerably in the last 20 years, making it difficult to compare prevalence and/or clonal size between different series of patients.

In some studies diagnosis was made by Ham or sucrose tests, in others by flow cytometry with monoclonal antibodies targeting CD55 and CD59. Finally, recent series have employed more sensitive reagents to detect more cases and quantify with greater precision the clonal size

Management [12, 13]

Treatment of BCS involves a stepwise approach depending on the severity of the clinical picture. The first

step consists in medical treatment and includes immediate anticoagulation plus diuretics and hydrosaline restriction as needed.

A second step includes endovascular unblocking procedures such as angioplasty ± stenting (for segmental occlusions) or thrombolysis. The next step is a transjugular intrahepatic porto-systemic shunt (TIPS) placed by endovascular approach.

Finally, for refractory patients, the last resource is a liver transplantation.

Furthermore, the therapeutic options for PNH have recently been extended with the discovery and development of eculizumab, a humanized monoclonal antibody directed against complement component C5. Treatment with this complement inhibitor has greatly reduced hemolysis and the severity of anemia in patients with PNH. Moreover, the rate of thromboembolic events was significantly lower survival curve of BCS patients with and without PNH

Mortality in patients with PNH is for a large part due to thrombotic complications and approximately 20% of all deaths can be attributed to BCS. Especially for patients with BCS it has been suggested that the presence of PNH is associated with a poor prognosis, with mortality rates as high as 67%.

Table 5: Stepwise Therapeutic Approach to BCS

1st Step	Medical treatment: hydrosaline restriction + diuretics + anticoagulation
2nd Step	Angioplasty ± Stenting ± thrombolysis
3rd Step	TIPS
4th Step	Orthotopic liver transplant

CONCLUSION

PNH is an exceedingly rare acquired disorder of haematopoietic stem cells. Our patient is followed regularly in our consultation and her prognosis is good so far even in the absence of etiological treatment of HPN (lack of material means) whose prognosis is a little bleak.

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