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CASE REPORT

# Paroxysmal nocturnal haemoglobinuria with Budd Chiari syndrome and Myelofibrosis

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**ABSTRACT**

We report a case of paroxysmal nocturnal haemoglobinuria (PNH) in a 38-year-old Indian female, who was admitted to our hospital with abdominal distension of 2-weeks duration, with leg oedema and jaundice. Her medical history was remarkable for deep vein thrombosis 15 years back, and stroke, nine years before admission. On clinical examination, spleen and liver were palpable, along with evidence of shifting dullness on abdominal percussion. Bone marrow examination showed hypoplastic bone marrow with agnogenic myeloid metaplasia, with myelofibrosis. Acidified serum lysis (Ham test) and sucrose lysis tests were strongly positive. The diagnosis of PNH was confirmed by flow cytometry. The patient could not be followed further, as she left for her country.

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**Key Words:** Budd-Chiari Syndrome; Myelofibrosis; Paroxysmal nocturnal haemoglobinuria

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## Introduction

PNH is an acquired haemopoietic stem cell disorder, characterized clinically by chronic haemolytic anaemia, with acute episodes, thrombosis, and bone marrow failure. It is a rare condition, which usually occurs in younger people. Immunophenotyping and flow cytometry play a key role in confirming the diagnosis of PNH. Treatment is mainly supportive. Since the disease is uncommon, delay in diagnosis often lead to deleterious effects on patient management and prognosis. We present this case to draw attention to this rare cause of Budd chiarii syndrome and Myelofibrosis, which should be considered in any patient of any age, who has signs of hepatic vein thrombosis..

## Case History

A 38-year-old Indian female visitor to Doha was admitted to our hospital with abdominal distension of 2-weeks duration, with leg oedema and jaundice. Her condition started three years ago with pain and abdomen distension that progressed gradually; and was diagnosed as liver cirrhosis. Past medical history was remarkable for deep vein thrombosis 15 years back, and stroke, nine years before admission. On examination, she had jaundice, clubbing of fingers, spider nevi, and leg oedema. Abdomen examination showed hepatomegaly with liver span of 15 cm, and splenomegaly, 6 cm below the costal margin, with positive shifting dullness. The results of investigations are presented in [Table/Fig 1]. Peripheral smear picture is presented in [Table/Fig 2].

Ultrasound abdomen showed cirrhotic liver with echogenic thrombus in the intrahepatic segment of IVC, with ascitis [Table/Fig 3]. Upper endoscope showed oesophageal Varices grade 2. In view of the above findings, hypercoagulable state was highly suspected, and thus, the following tests were requested: Anti thrombin function, protein C and S factor. V Leiden and homocysteine were normal. Anticardiolipine IGg and IgM levels were within normal limits. Bone marrow examination showed hypoplastic bone marrow with Agnogenic Myeloid Metaplasia, with Myelofibrosis [Table/Fig 4]. Acidified serum lysis (Ham test) and sucrose lysis test were strongly. To confirm

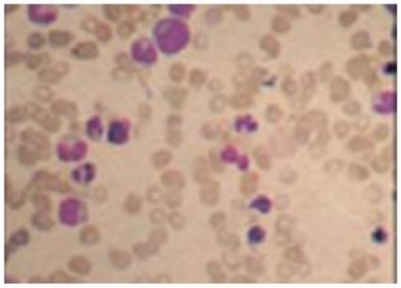
the diagnosis, flow cytometry was performed, which showed a deficiency of CD59 and CD55 on red cells. Thus, the patient was diagnosed with PNH complicated with Budd Chiarii syndrome (BCS) and myelofibrosis. The patient was treated symptomatically by blood transfusion, Iron, folic acid, and diuretic. The patient was discharged against medical advice, and she left the country forever.

**Table/Fig 1**

**Investigations During admission**

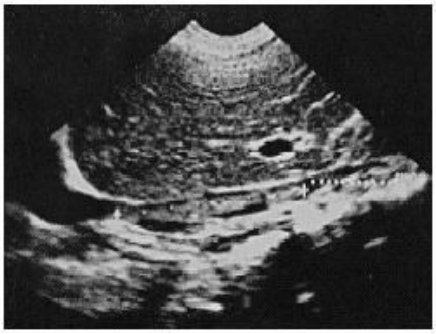
| Parameter | Result | Parameter | Result |
|---|---|---|---|
| Hemoglobin | 5.4 gm/dl | Sugar | 5.2 mmol/l |
| MCV | 98.4fl | Creatinine | 45mmol/l, |
| MCH | 27.2pg | Urea | 2 mmol/l |
| MCHC | 26.5g/dl | HCO3 | 19 mmol/L |
| Total leukocyte | 1500/µL | Bilirubin | 67 µmmol/l(N<24) |
| Neutrophil | 51% | Direct bilirubin | 38mmol/l, |
| Lymphocyte | 34% | Albumin, | 29g/l |
| Eosinophils | 7% | Protein | 60gm/l, |
| Monocyte | 8% | alkaline phosphates | 218u/l, |
| Platelet | 34,000/uL | AST | 59u/l |
| Prothrombine time | 16 second ( 9-11) | ALT | 46 u/l |
| International ratio | 1.4 | Alfa fetoprotein | Normal |
| Activated partial prothrombine time | 33.6 seconds(normal) | TIBC | 50µmol/l |
| Iron level | 2µmol/l | Iron saturation | 2.9% |
| Peritoneal fluid analysis showed: protein 26g/l, Albumin of 11g/l with albumin gradient of 1.8 g/dL, white blood cell count of 212/µL, neutrophil of 37% and lymphocyte of 59%, sugar normal and no malignant cell on cytology | | | |
| Hepatitis serologies, antinuclear antibody, anti smooth muscle antibody and anti mitochondrial antibody were negative | | | |
| Urine Hemoglobin was positive. Coombs test negative, reticulocyte count was normal, and haptoglobuline level was low<0.12mmol/l, LDH was high 7612u/l (N<455); G6PD and Hemoglobin electrophoresis were normal | | | |

**Table/Fig 2**



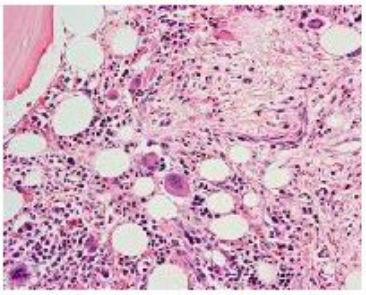
**Myelofibrosis; peripheral blood showing teardrop poikilocytes, basophilic stippling and a myelocyte.**

**Table/fig 3**



**Echogenic thrombus in the intrahepatic segment of the IVC.**

**Table/Fig 4**



**Bone marrow showed Agnogenic Myeloid Metaplasia with Myelofibrosis.**

## Discussion

PNH is characterized by intravascular haemolysis, venous thrombosis, and an association with aplastic anaemia [1].PNH arises through a somatic mutation of the phosphatidylinositolglycan complementation class A (PIGA) gene in a haematopoietic stem cell, and the expansion of the abnormal haematopoietic clone. PIGA encodes a protein involved in the first step of glycosylphosphatidylinositol (GPI) biosynthesis [2].GPI structures anchor a wide variety of proteins to the cell surface via their lipid moiety. Deficiency of GPI-linked proteins from PNH erythrocytes can be complete (PNH type III cells) or partial (PNH type II cells). The terminology is derived from different complement lysates, sensitivities of the 3 types of PNH erythrocytes, type III being 15 to 25 times more sensitive to complement than normal cells [3].

This variability in the severity of the deficiency, as well as in the proportion of the affected cell population, defines the clinical manifestations of the disease [4-5]. Classical PNH is diagnosed if patients have high LDH and indirect bilirubin with very low concentration of serum haptoglobin, without evidence of any defined bone marrow abnormality. [6] But our patient had all these abnormal investigations along with myelofibrosis, and therefore she can be classified as PNH, in the setting of another bone disorder i.e. myelofibrosis. PNH is a disease of adults presenting in the 3rd to 5th decade of age. In a large series of 78 cases of PNH diagnosed in 10 years, the mean age of diagnosis was 34 years. [7] Age of our patient was 38 years during the diagnosis, which is a common age for this condition.

PNH is associated to venous thrombosis in approximately one third of cases. [8] Venous thrombosis most often occurs in the intra abdominal veins, particularly the hepatic veins.

[9-11] PNH results in thrombosis of hepatic veins, leading to hepatic obstruction, thereby increasing the risk of developing BCS in patients. Presenting complaints of many BCS patients were reported to be abdomen pain, distension, and oedema of lower limbs. [12] Our patient also presented with similar complaints. In the series of 78 cases of PNH by Zhao et al, Ham's test was positive in 65.8% cases, whereas CD59 and CD55 were found deficient in 100% of cases. [7] Although both the acidified serum lysis test (Ham test) and the sucrose lysis test (sugar water test) have much biologic and historic importance, they have largely been abandoned as diagnostic assays, because they are both less sensitive and less quantitative than flow cytometry. In our patient, flow cytometry confirmed the deficiency of CD55 and CD59.

The onset of hepatic vein thrombosis in PNH may be insidious or sudden, which is frequent in the setting of a haemolytic episode.[13] Our patient had multiple attacks of thrombosis as DVT and CVA in the past before the attack of BCS, secondary to involvement of the hepatic vein. PNH has been described in the setting of Myelodysplastic (MDS) or myeloproliferative disorders [14- 17], with an incidence ranging from 5 to 9 percent [18] . In a reported study of 44 patients with BCS, almost 7 (6%) patients had myeloproliferative disorders as a causative factor [12]. Our patient also had features of Myelofibrosis, as seen by blood film analysis, which showed tear-drop poikilocytes, basophilic stippling and a myelocyte, in addition to the bone marrow finding showing hypoplastic bone marrow with Agnogenic Myeloid Metaplasia with Myelofibrosis, which might have been a causative factor for BCS, along with PNH. The presence of both myelofibrosis and PNH might have enhanced the chance of BCS developing in our patient.

Treatment is based upon presenting symptoms. Iron and folic acid supplements help replace losses due to haemolysis. Until recently, allogeneic bone marrow transplantation was the only effective therapy for these patients; however, the development of eculizumab now offers them great hope. Alternate-day prednisone therapy is occasionally helpful in ameliorating haemolysis in PNH, but most patients show little or no response to this treatment. [19]. Our patient received iron and folic acid supplements.

## Conclusions

Although rare, PNH and Myelofibrosis should be considered in the differential diagnosis of Budd Chiari syndrome.

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