

# Paroxysmal Nocturnal Hemoglobinuria

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## ABSTRACT

Paroxysmal Nocturnal Hemoglobinuria (PNH) literally means to have episodes of hemoglobin in the urine during the night. It is a Coomb's negative rare hemolytic disorder characterized by non-malignant clonal expansion of haemopoietic stem cells due to acquired genetic mutations. A 30 years old male patient presented with 5 years history of transfusion dependent anemia with intermittent episodes of passing dark colored urine in the morning. Blood complete picture showed decreased hemoglobin and reticulocytosis upto 30%. Coomb's test was negative with unconjugated hyperbilirubinemia and markedly raised serum LDH. Urine analysis showed marked hemosiderinuria and flow cytometry revealed 60% RBCs deficient for CD-59, confirming the diagnosis of paroxysmal nocturnal hemoglobinuria. The management of the patient depends on whether anemia is due to hemolysis or as consequence of impaired erythropoiesis. Corticosteroids at a dose of 0.25-1 mg/kg/day was selected as it is amongst the various treatment options in patients with predominant hemolysis.

**Key words:** *Paroxysmal nocturnal hemoglobinuria. Hemolysis. Anemia.*

## INTRODUCTION

Anemia is a common diagnosis in routine medical practice treated with heamatinic supplements without probing into the underlying etiology. Hemolytic anemia is amongst the diverse subtypes of anemia, which require extensive laboratory work-up to establish the diagnosis. Paroxysmal Nocturnal Hemoglobinuria (PNH), which literally means to have episodes of hemoglobin in the urine during the night, is a rare hemolytic disorder characterized by non-malignant clonal expansion of haemopoietic stem cells due to genetic mutations.<sup>1</sup> Intravascular hemolysis is the primary clinical manifestation of PNH, which may be associated with marrow failure and/or thrombophilia, causing significant morbidity and mortality.<sup>2</sup> We came across one such case being treated for anemia who had received multiple blood transfusions.

## CASE REPORT

A 30-year old male patient presented with 5 years history of progressive weakness, lethargy and episodic abdominal pain. He also had intermittent episodes of passing dark colored urine in the morning, which was exacerbated by prolonged traveling. He received more

than 15 transfusions over the last 5 years for his above symptoms, which were attributed to anemia, however, no investigations were done to determine the underlying etiology. His clinical examination revealed marked pallor and lemon tinged appearance. However, no hepatosplenomegaly, rash or lymphadenopathy was seen. The laboratory work-up showed hemoglobin of 2.6g/dL, total leucocyte count of 2.5x10<sup>9</sup>/L and platelet count of 183x10<sup>9</sup>/L. His morphological indices showed a PCV of 9.3% and MCV 104.5 fL. Peripheral film reticulocyte count was 30%. A bone marrow examination revealed a hypercellular marrow with megaloblastic changes, dyserythropoiesis and absence of iron in the marrow. A provisional diagnosis of hemolytic anemia was made and further investigations were done to determine the cause. His serum total bilirubin was 47µmol/L while direct bilirubin was 11µmol/L. He had a markedly raised serum lactate dehydrogenase levels of 2815 IU/L, while Coomb's test was negative and no RBC sickling was seen on sickling test. The urine showed marked hemosiderinuria. Keeping in view marked hemosiderinuria in a Coomb's negative hemolytic anemia, flow cytometry was done for CD-59, which revealed 60% RBCs deficient for CD-59 (Figure 1). This was highly suggestive of PNH. He was prescribed corticosteroids at a dose of 1mg/kg/day along with hematinics and gastro-protective agents. His transfusion dependency decreased and hemoglobin rose to 10.6 g/dL after 3 months.

## DISCUSSION

Hemolytic anemia is a diverse group of intra and extravascular disorders mainly including RBC wall defects, hemoglobin chain abnormalities, enzymatic deficiencies immune and non-immune mediated hemolysis. PNH is a complement mediated hemolytic

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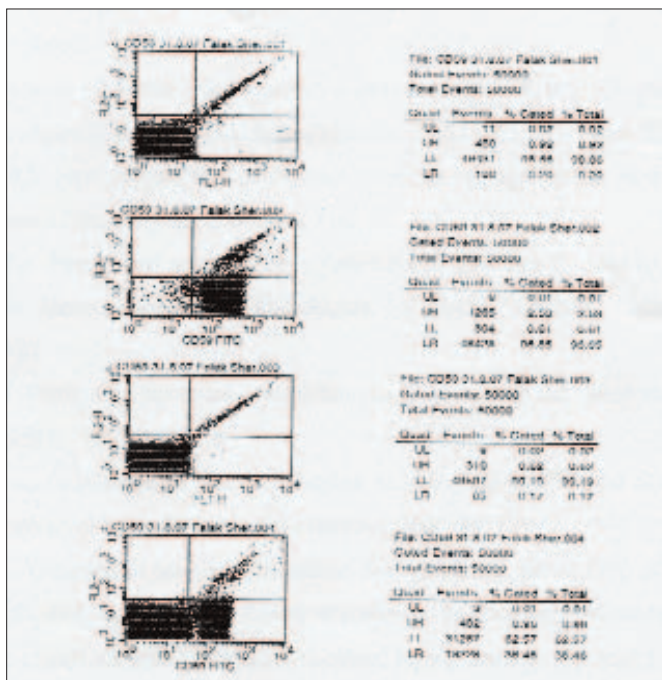


Figure 1: Flow cytometric analysis showing peripheral red blood cells deficient for CD-59.

disorder, which occurs due to the deficiency of glycosyl phosphatidylinositol-anchored proteins (GPI-APs), anchored complement regulatory proteins CD-55 and CD-59.<sup>2</sup>

Patients with PNH classically report with gross hemoglobinuria and symptoms of anemia. GI complaints like episodic abdominal pain and dysphagia can be the initial complaints in approximately 10% of patients. Hemorrhagic signs and symptoms, aplastic anemia, infections, thrombosis, and neurological sequel may also be seen at presentation.<sup>3</sup> Patients presenting with thrombosis at unusual sites and co-existent cytopenia and intravascular hemolysis should be screened for PNH. However, routine screening in all patients of thrombosis is not recommended.<sup>4</sup>

Coomb's negative hemolytic anemia is the clinical hallmark of PNH.<sup>5</sup> The disease arises in the setting of bone marrow abnormality and hemolysis may be part of the process in patients with anemia. The minimal essential criteria required for the diagnosis includes deficiency of GPI-APs either in erythrocytes, granulocytes or preferably both. This deficiency may be partial rather than complete and flow cytometric analysis using antibodies against CD-59, is the most sensitive and informative assay for its diagnosis.<sup>6</sup>

PNH is divided into three subtypes on the basis of marrow and flow cytometric studies. In classical PNH, there is evidence of intravascular hemolysis by reticulocytosis, abnormally low concentration of serum haptoglobin and high levels of serum lactate dehydrogenase as was seen in our case. Another subtype presents with concomitant underlying bone

marrow abnormality in the form of aplastic anemia, myelodysplastic syndrome or myelopathy. A rare sub-clinical PNH has neither clinical/ laboratory evidence of hemolysis nor GPI-APs deficient hemopoietic cells on flow cytometry and is associated with a few cases of aplastic anemia and refractory anemia-MDS.<sup>2</sup>

The management of a patient with PNH depends on whether anemia is due to hemolysis or as a consequence of impaired erythropoiesis. Treatment is indicated to improve the quality of life and prevent untoward effects of chronic hemolysis on renal functions in those patients who have hemolysis as the predominant factor to anemia.<sup>7</sup> Corticosteroids at a dose of 0.25-1 mg/kg/day is amongst the various treatment options in patients with predominant hemolysis.<sup>3</sup> However, it is a subject of debate since some members of International PNH group do not advocate its use under any circumstances. The main value of steroids has been in attenuating acute exacerbations. Brief pulses of prednisolone reduce the severity and duration of crisis avoiding untoward effects associated with long-term use.<sup>2</sup> Androgen therapy, either alone or in combination with steroids, has also been used with success but monitoring of liver functions is mandatory in such patients.

Supplemental iron and folates are recommended as adjunct to cater for their deficiency as a result of hemoglobinuria and hemosiderinuria in these patients. Transfusions ameliorate hemolysis by suppressing erythropoiesis. On the other hand, a patient of PNH with anemia and primary marrow failure, and who has been receiving multiple transfusions, may end up with iatrogenic hemochromatosis due to iron overload.<sup>2</sup> Treatment of anemia due to primary marrow failure should be aimed at underlying marrow disease.

Since PNH is a complement mediated cytolysis, inhibition of complement using monoclonal antibodies against complement C-5 (Eculuzimab) is being studied. Both an initial pilot study and two phase III clinical trials of eculuzimab have dramatically reduced intravascular hemolysis, hemoglobinuria, and transfusion requirements thus improving the quality of life in patients with PNH.<sup>8</sup> Stem cell transplantation is also being evaluated and multicentre trials have shown an increased median survival.<sup>9</sup>

To conclude, PNH is a rare disorder which should be considered in the differential diagnosis of a patient with cytopenia and high reticulocytes. Coomb's negative hemolytic anemia is the hallmark of PNH.

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