

## Paroxysmal Nocturnal Hemoglobinuria-A Case with Renal Manifestation

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### Abstract

PNH arises from a somatic mutation involving a gene on the X chromosome which codes for a protein involved in the formation of phosphatidylinositol glycan (PIG A), which anchors many proteins to the surface of cell membranes. The deficiency of PIG leads to reduced levels of Decay accelerating factor (DAF, CD55) and Membrane inhibitor of reactive lysis (MIRL, CD59), both responsible for inactivation of complement. This in turn leads to increased sensitivity of PNH red cells to lysis. It is an acquired clonal disorder characterized by a triad of clinical features of hemolytic anemia, pancytopenia, and thrombosis. Not many reports of renal involvement in PNH are available in literature. We present a case report of PNH with renal involvement.

**Keywords:** PNH; Hemolytic Anemia; DAF; MIRL

### Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal disease of bone marrow stem-cells and is genetically characterized by the somatic mutation in the phosphatidylinositol glycan protein A (PIG-A) gene, which is located on the short arm of X chromosome. This gene is essential for the formation of glycosylphosphatidylinositol (GPI), which is responsible for anchorage of certain proteins that regulate the complement system in the outer cell membrane surface of erythrocytes, leukocytes and platelets, such as complement decay-accelerating factor (DAF, CD55) and membrane inhibitor of reactive lysis (MIRL, CD59) [1,2] Hence deficiency of proteins CD55 and CD59 and of the GPI anchor in PNH cells make them sensitive to lysis from complement, causing intravascular hemolysis. Depending on the degree of sensitivity to complement, three different types of red cells are found in PNH:

1. PNH1: Red cells with normal sensitivity to complement;
2. PNH2: Red cells with intermediate sensitivity to complement mediated lysis;
3. PNH3: Red cells with marked sensitivity to complement mediated lysis.

International PNH Interest Group (I-PIG) includes three main categories that cover the spectrum of disease presentation and proposed a classification scheme for PNH [3]:

- Classical PNH, which includes haemolytic and thrombotic patients.
- PNH in the context of other primary disorders, such as aplastic anaemia (AA/PNH) or myelodysplastic syndrome (MDS/PNH).
- Subclinical PNH (scPNH), in which patients have small PNH clones but no clinical or laboratory evidence of haemolysis or thrombosis.

The diagnosis of PNH is done by clinical findings and laboratory tests along with ancillary tests like, haptoglobin, lactate dehydrogenase, direct Coombs test, reticulocyte count, total bilirubin and deficiency of anchored proteins of the complement system CD55, CD59 (Red blood cells), CD15, CD33 and CD24 (granulocytes) and CD14 and CD64 (Monocytes) by flow cytometry. Initially PNH was diagnosed by Ham test, sucrose haemolysis test and complement lysis assay. Currently, these methods are no longer used. The gold standard diagnostic method in PNH is flow cytometry, which evaluates the presence of CD55 and CD59 and other GPI-linked proteins in red blood cells, granulocytes and monocytes membranes. This test presents high sensitivity and specificity [4-6].

Paroxysmal Nocturnal Hemoglobinuria usually presents during third and fourth decades of life with features of chronic hemolytic anemia, weakness and mild jaundice. Nocturnal hemoglobinuria is seen in few cases which is due to increased hemolysis during sleep. Hemosiderinuria is a feature which leads to iron deficiency anemia. Recurrent venous thrombosis is a common feature.

Renal involvement in PNH is rare and is first recognized in early 1970 [7]. Literature search revealed that there is paucity of cases of Paroxysmal nocturnal hemoglobinuria with renal involvement. Here we present a case of patient who had anemia, thrombocytopenia and hemoglobinuria with renal involvement which on further work up diagnosed as paroxysmal nocturnal hemoglobinuria.

### Case Report and Discussion

42 years old female presented with the complaints of weakness, fever, pain abdomen, hematuria, palpitation and low urine output since 2 days. Her past history revealed jaundice 7 years back for that she was transfused with a single unit of blood. She had one abortion 5 years back.

There is no history of renal stones, NSAID abuse, weight loss, night sweats, malena or hemoptysis. Her vital signs were unremarkable.

On initial evaluation her complete blood count was as follows:

- WBC count 4,200/cu mm, hemoglobin 8.1 g/dL, platelet count 1,10,000/ cu mm.
- MCV 78 fl, RDW CV19.1, RDW SD61. Peripheral blood finding shows red blood cells as microcytic hypochromic with anisocytosis. Platelets shows thrombocytopenia and white blood cells morphology and counts were within normal limits.
- Biochemical parameters showed total serum bilirubin 1.7 mg/dl. AST- 33 U/L, ALT -46 U/L, serum LDH 1948 U/L, creatinine was 12.3 mg/dl. Hepatitis B surface antigen was negative, Hepatitis C antibody was negative. Indirect and Direct Coomb test were negative The urinalysis showed presence of dark brown colour urine with presence of hemoglobin, pyuria, sugar as trace and protein + 3.

As patient was having acute kidney injury with high creatinine and oliguric condition with no obvious cause of involvement to kidney and with history of anemia, hemoglobinuria, high LDH, we advised for further work up of hemolytic anemia specifically paroxysmal nocturnal hemoglobinuria.

However, when renal disease is significant, it usually manifests as acute kidney injury (AKI) and rarely as chronic kidney disease (CKD) [8].

With this history of AKI and hemolysis, renal biopsy was performed which showed the features of non-proliferative morphology in glomeruli with patchy acute tubular injury with extensive deposition of golden brown pigment granules in tubular epithelial cell cytoplasm which were positive for iron/hemosiderin pearl stain which shows the possibility of Paroxysmal nocturnal hemoglobinuria.

Direct Immunofluorescence studies showed immunoglobulin A, immunoglobulin G immunoglobulin M were negative. C3, C1q, kappa and lambda light chain were negative by ruling out possibility of all glomerulonephritis.

Further the EDTA blood sent for flow cytometry which showed PNH clone within the granulocytes with deficiency of CD 55 [87.7%], deficiency CD 55 in monocytes [85.9%], Type two red blood cell with partial CD 59 deficiency was 3.26% and Type three red blood cell

with complete CD 59 deficiency was 13.03%. Thus diagnosis of paroxysmal nocturnal hemoglobinuria was established.

Our case shows that PNH may present with AKI when hemolysis occurs and hemosiderin deposits in the renal tubular epithelial cells. Early diagnosis and treatment are crucial to prevent disease progression and irreversible CKD also we conclude the necessity and the importance of a multidisciplinary follow up of every patients.

### Conclusion

Etiopathogenesis of Paroxysmal nocturnal hemoglobinuria is based on acquired mutations that lead to the absence or reduction of CD55 and CD59 complement regulators, which are responsible for intravascular hemolysis, cytopenias and thrombosis. PNH is often

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