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CASE REPORT

A CASE REPORT OF THE FIRST CONFIRMED PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) IN ETHIOPIA

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ABSTRACT

PNH is an acquired hemolytic disorder caused by somatic mutation characterized by intravascular hemolysis with pancytopenia and a tendency to thrombosis. It is a rare disease with incidence of 1 to 10 cases per million populations. We are reporting the first confirmed case of PNH in Ethiopia. He is a 38 years old man who presented with anemia and jaundice of 3 years duration; he has mild pallor; lab examinations showed moderate anemia with features of Coomb's negative intravascular hemolysis; and finally very large clone of PNH cells on immunophenotypic analysis.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare benign clonal acquired hematopoietic stem-cell (HSC) disorder caused by somatic mutation of X-linked phosphatidylinositol glycan class A (PIGA) gene which can arise de novo or in the setting of acquired bone marrow (BM) failure. The product of PIGA gene is required for synthesis of anchor protein that ties other proteins to the cell surface known as glycosylphosphatidylinositol (GPI-anchor).

The two GPI-anchored proteins (CD55&CD59) normally function as complement regulatory proteins; absence or deficiency of which makes cells exquisitely sensitive to activated complement, whether it is activated through the alternative or classic pathway (1,3) The reported incidence of clinically significant disease is in the range of 1 to 10 cases per million populations, although this may be an underestimate as a subset of patients are likely to remain undiagnosed. It has been reported from almost every country in the world with no known ethnic or geographic distribution (2,3).

The classic triad of its presentation; hemolysis, pancytopenia and thrombophillia make it a unique clinical condition. Renal involvement in PNH is not usually apparent but in cases with clinical involvement varies from reversible acute dysfunction to chronic irreversible damage. Early diagnosis and treatment is crucial to prevent disease progression and irreversible chronic kidney disease (CKD) (2,3,5,6).

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Laboratory investigations suggesting the diagnosis of PNH includes the presence of anemia, hemoglobinuria, reticulocytosis, an elevated lactate dehydrogenase and undetectable haptoglobulin. Clinical diagnosis of PNH may be confirmed with peripheral blood flow cytometry demonstrating the absence or severe deficiency of GPI-anchored proteins on at least two cell lines. (3,4).

Here we are reporting a 38 years old male patient who is the first to have confirmed PNH in Ethiopia with acute reversible renal dysfunction; some of the challenges in diagnosis and management of such patients in resource poor settings like ours.

CASE SUMMARY

The patient is a 38 years old man who presented to our hematology referral clinic with gradually progressive symptoms of anemia, and intermittent yellowish discoloration of the eyes of 2 years duration. He has no constitutional symptoms, bleeding from any site, body swelling, previous known medical illness, or family history of similar illness. Initially with the consideration of megaloblastic anemia he was treated with folic acid and vitamin B12 with no satisfactory response. Bone marrow aspiration was done which was nonrevealing. While he was on follow up he developed severe loin pain which was sudden with associated dark urine, generalized body swelling and decreased urine output. Work up revealed acute kidney injury which requires six sessions of hemodialysis and renal function recovered.

The basic laboratory tests show mild normocytic normochromic anemia with evidences of intravascular hemolysis (WBC- 3500/µL with 63% neutrophils, hemoglobin and hematocrit- are 10.8 g/dl and 36.9% respectively with MCV of 85 Fl, the total bilirubin was 3 g/dl with direct of 0.3 g/dl, the reticulocyte count was 339*103/µL (4.5%) and comb's test is negative and the serum LDH is 3522 IU/L). The serology for HBSAg, HCV Ab, retroviral infection, ANA, and Anti dsDNA were all negative. Urine dipstick shows blood ++ and microscopy was unremarkable.

Imunophenotypic analysis were sent from the peripheral blood for PNH panel and showed discrete populations of neutrophils, monocytes, and red cells which lack expression of GPI- linked markers which is summarized as follows.

Table 1: PNH panel

Cell lines (GPI anchored proteins)	% of PNH clone
Neutrophils (CD24, CD55, CD59)	99.5
Monocytes (CD14)	99.2
Red blood cells (CD59)	90.8

Of the whole red cells 51.4 % were type III cells i.e. with complete deficiency and 39.4% were type II cells i.e. with partial deficiency of GPI anchored proteins. The conclusion was very large clone size (99%) is present. A diagnosis of Classical PNH was made after excluding other possible causes of a process of intravascular hemolysis. Short of access to terminal complement inhibitor (eculizumab) he was started on prednisolone10 mg po daily with folate and iron supplementation and the patient is stable subsequently.

DISCUSSION

PNH is a non-neoplastic human disease caused by a somatic mutation of the X-linked phosphatidylinositol glycan-complementation class A (PIGA) gene in hematopoietic stem cells which makes red blood cells vulnerable to lysis mediated by complement due to deficiency or absence of complement regulatory proteins which are GPI-anchored; the most important being CD59 and to a lesser extent CD55 (1,3,40. PNH is a rare disease entity which has a prevalence of 1-10 cases per million people. It has about the same frequency in men and women. (1,2) Although PNH is reported in all age groups, the peak incidence is in the third and fourth decades of life (2,3). Patients with PNH suffer a range of symptoms and complications, which almost all result from haemolysis.

The clone size and the status of the bone marrow dictate the range and severity of symptoms. The primary clinical manifestations of PNH are hemolysis, thrombosis, and marrow failure. Constitutional symptoms dominate the history, with nocturnal hemoglobinuria being a presenting symptom in only approximately 25 percent of Patients. Other nonspecific symptoms include episodic dysphagia and odynophagia, abdominal pain, and male impotence due to smooth muscle dystonia. Venous thrombosis, often occurring at unusual sites (Budd-Chiari syndrome, mesenteric, dermal, or cerebral veins), is the most common cause of mortality to be followed by infection and bleeding from associated bone marrow failure. Arterial thrombosis is less common. (2,3,5).

Acute kidney injury (AKI) can be induced by the release of heme pigments during times of very intense intravascular haemolysis and haemoglobinuria which may require dialysis but potentially fully reversible. The incidence of AKI related to hemolysis is not well described, but may be as high as 50% with massive hemolysis (5,6).

PNH should be suspected in all patients with non-spherocytic, Coombs-negative intravascular hemolysis. The most consistent blood finding is anemia with other features of intravascular hemolysis. (3,5). The diagnosis of PNH is confirmed with peripheral blood flow cytometry by detecting the absence of GPI-anchored proteins on ≥ 2 lineages with a reagent known as fluorescent aerolysin (FLAER) and diagnosis will be made if first approximation at least 5% of the total red cells and at least 20% of the total granulocytes should be detected (1,3-5).

Through improved diagnostic techniques, it has been possible to differentiate subgroups of PNH: Classic PNH, PNH in the setting of another specified bone marrow disorder and Subclinical PNH. (3). The treatment of PNH depends on the severity of symptoms and consists of supportive treatment which includes transfusion support, hematinics, and anticoagulation; and immunosuppressive treatment which include terminal complement inhibitor like eculizumab which is the only FDA approved drug for the treatment of PNH or steroid and hematopoietic stem cell transplantation which is the only curative therapy for PNH (3,8,9). The cost of eculizumab, trade name Soliris®, is approximately 409,500 USD per year, making it one of the most expensive drugs in the United States (10). The extremely high cost of the drug makes its use in PNH in resource-constrained countries almost unjustified.

Coming to our patient he presented with only symptoms of anemia which is not uncommon to find with typical age group and full-blown features of intravascular hemolysis. He has delayed diagnosis due to his nonspecific presentation and due to initial incomplete workup. During one episode of exacerbation he had also dialysis requiring renal dysfunction which has completely recovered. Finally he had classical PNH defined by confirmed PNH clone and intravascular hemolysis with no evidence of other bone marrow abnormality.

He has very large clone of PNH cells and he could have benefited from eculizumab which is very expensive and not available in this country. Even though steroids are not recommended due to lesser efficacy and long-term toxicity, it is the only option available in this country.

In our country there is not any previously reported case of PNH with some reports in some other African countries (7).

In summary we should consider PNH in the appropriate clinical scenario and work up patients for early diagnosis, proper management and follow up of symptoms and some unique and fatal complications associated with it. In a resource limited settings standard of care for such patients is mainly supportive with the use of hematinics and with the appropriate transfusion of blood products.

Competing interests

The authors declare that this manuscript was approved by all authors in its current form and that no competing interest exists.

REFERENCES

1. Luzzatto L, Bessler M, Rotoli B: Somatic mutations in paroxysmal nocturnal hemoglobinuria: a blessing in disguise? Cell. 1997; 88(1):1–4.
2. Screzenmeir H, Muus P, Socie G, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Hematologica 2014; 99:922.
3. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 2005; 106: 3699-3709.
4. Fletcher M, Sutherland DR, Whitby L, et al. Standardizing Leucocyte PNH clone detection: An international study. Cytometry B Clin Cytom 2014. Accessed at https://doi.org/10.1002/cyto.b.21174.
5. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995; 333: 1253-58.
6. S. Hussain, A. Qureshi, J. Kazi: Renal involvement in paroxysmal nocturnal hemoglobinuria. Nephron Clin Pract 2013; 123:28–35.
7. Garrick Laudin, Lizemarie Wium: A case of paroxysmal nocturnal hemoglobinuria (PNH) in an obstetric patient: A South African perspective. CMI 2019; 13(1). DOI: 10.7175/cmi.v13i1.1392.
8. Issaragrisil S, Piankijagum A, Tang-naitrisorana Y: Corticosteroids therapy in paroxysmal nocturnal hemoglobinuria. Am J Hematol 1987; 25: 77-83.
9. McKeage K: Eculizumab: a review of its use in paroxysmal nocturnal haemoglobinuria. Drugs. 2011; 71(17): 2327–45.
10. Dinerstein C. Why Is Soliris the Most Expensive Drug In The US? American Council in Science and Health. May 27, 2017. Available at https://www.acsh.org/news/2017/05/27/why-soliris-most-expensive-drug-us-11333.