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"PNH AS PRONOUNCED PERSISTENT PANCYTOPENIA WITH HYPERCELLULAR MARROW SIMULATING MEGALOBLASTIC ANEMIA – A RARE PRESENTATION OF A RARE DISEASE"

General Medicine

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ABSTRACT

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare form of chronic hemolytic anemia caused due to an acquired defect in PIG-A (Phosphatidylinositol-N-acetyl glucosanilyl transferase-subunit-A) gene. The mutation of this gene lead to deficiency of anchor proteins (complement regulating proteins) which are normally present on RBC membrane and prevent RBCs from the complement mediated destruction (CD55 and CD59 – Decay Accelerating Factor and Membrane Inhibitor of Reactive Lysis, respectively). Deficiency of these proteins in PNH make blood cells more susceptible to lysis by complement system. We describe the case of a 35 years old male who presented to Medicine Department, J.A. Group of Hospitals, Gwalior (M.P.) for anemia and we later diagnosed him as PNH (via flowcytometry). Current treatment guidelines recommend the use of Eculizumab and Ravulizumab (anti-C5) but the cost and availability of the treatment is a major limiting factor in developing countries like India.

KEYWORDS

PNH, Anemia, Hemolytic, Flowcytometry

INTRODUCTION

Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired form of chronic hemolytic anemia characterized by intravascular hemolysis. In addition to (i) hemolysis, there may be – (ii) aplastic marrow causing pancytopenia, (iii) tendency for venous and arterial thrombosis.[1] It has a worldwide incidence of 5-6 cases per million and prevalence of 16 cases per million. The mean age at diagnosis is 50 years with SD of 18.6.[2] Although the literature contains a lot of information on PNH, the disease is a rare diagnosis in routine clinical practice.

Patients who present with Coombs negative hemolytic anemia, aplastic anemia, refractory anemia and unexplained thrombosis, co-occurring with cytopenia or hemolysis are generally screened for PNH.[3]

Flowcytometric evaluation of peripheral blood for GPI anchored protein in at least 2 lineages (red and white cells) is the gold standard for diagnosis. It is the most sensitive and reliable diagnostic test that confirms the presence and even quantify the PNH clone.[4]

However, the varied and atypical presentation of this rare disease make it challenging for physician to diagnose it.

It takes close to 2 years and often multiple providers to correctly diagnosed PNH.[5,6] Fewer than 40% patients with PNH receive this diagnosis within 12 months of symptoms onset, and 24% of all PNH diagnosis can take even 5 years or longer.[6]

The only therapies approved for PNH (by US-FDA) are anti C5 (complement inhibitory drugs) – Eculizumab (2007) and Ravulizumab (2018).[7-9]

The only permanent cure for PNH is an allogenic Hematopoeitic Stem Cell Transplantation (HSCT) but it is associated with higher mortality (as high as 42% at 12 months).[3]

Additional treatment are inclusive of supportive management and prevention of complication of PNH, such as blood transfusion/ iron replacement/anticoagulant to reduce risk of thrombosis and supplementation with folate/iron/B12 to support erythropoiesis in the marrow.

We aim to present this case keeping in mind the rarity of the disease, its varied presentation in clinical setting and the difficulty in its diagnosis.

Case Presentation

Informed consent was obtained from the patient and his family for this case report.

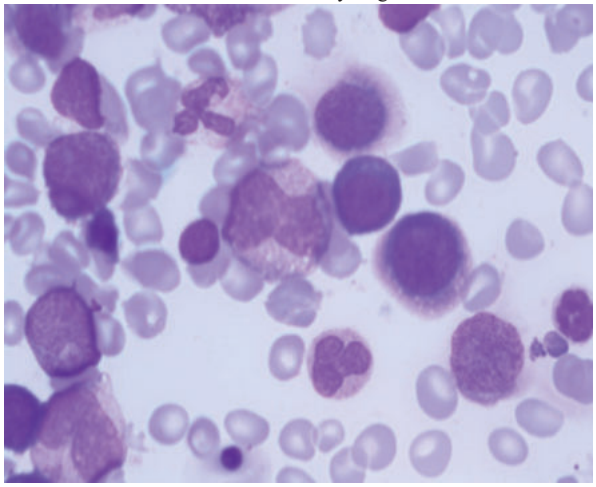
A 35 years old male presented for first time in December 2019 with chief complaint of fatiguability and generalized weakness for past 1-2 months. The patient had no complaint of dark urine/hematuria, fever, jaundice, weight loss, drug abuse or anorexia. He had no significant past medical, family or drug history. He was always in completely good health prior to this. His vitals were stable. On examination, the only significant clinical finding was pallor (over skin and mucous membrane). No splenomegaly/jaundice could be appreciated.

History of multiple admissions and multiple blood transfusion was present for the similar complaints.

Routine hematological investigations on sequential basis are summarized in the table below. Reticulocyte count was raised but the Reticulocyte production index (RPI) was less than 2. Peripheral blood smear showed macrocytes with pancytopenia and polychromasia. BT/CT/PT were normal, serum bilirubin and LDH levels were within normal limits. No evidence of hemolysis was observed. Urinalysis was normal. Urine and stool samples for blood were negative.

Bone marrow examination showed hyperplastic marrow with erythroid hyperplasia with megaloblastic changes, this gave us a suspicion of megaloblastic anemia (B12/folate deficiency). But, the vitamin B12 and folic acid levels in blood were found to be normal on subsequent investigations.

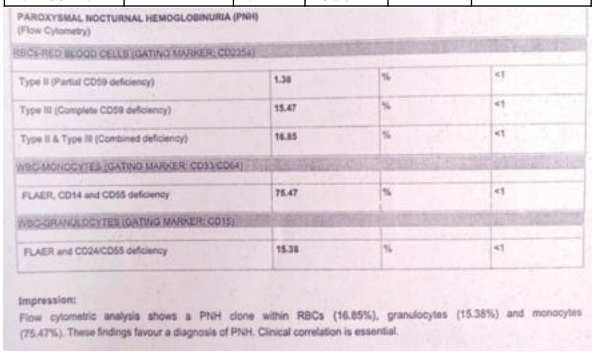
He was started on B12/folate/iron therapy but the pancytopenia was unresponsive to this therapy. He had multiple admissions for recurrent pancytopenia. Keeping in mind the variable and rare presentation of PNH as megaloblastic anemia with pancytopenia with hypercellular marrow which was refractory to other therapies, flowcytometry for PNH was advised and the case was finally diagnosed as PNH.



Bone Marrow Findings Suggestive Of Megaloblasts With Erythroid Hyperplasia With Hypercellular Marrow

Sequential Hematological Findings

Date	RBC count (million/cumm)	Hemoglobin (g/dl)	WBC count (/cumm)	Platelet count (/cumm)	Reticulocyte count (%)
13 June 2020	1.68	5.9	2100	30 K	4.2
14 July 2020	1.71	6.2	1900	60 K	
29 Aug 2020	0.93	3.8	1700	40 K	
1 Sept 2020	1.51	5.6	2100	64 K	
3 Sept 2020	1.84	6.7	1900	40 K	
15 Jan 2021	2.55	7.7	2800	54 K	6.8
4 Feb 2021	2.85	6.7	2400	60 K	
19 Feb 2021	1.5	4.6	2100	60 K	5.4
20 Feb 2021		4.4	1800	42 K	



PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)
(Flow Cytometry)

RBCs-RED BLOOD CELLS (GATING MARKER: CD235a)			
Type II (Partial CD59 deficiency)	1.38	%	<1
Type III (Complete CD59 deficiency)	15.47	%	<1
Type II & Type III (Combined deficiency)	16.85	%	<1
WBC-MONOCYTES (GATING MARKER: CD33/CD64)			
FLAER, CD14 and CD55 deficiency	75.47	%	<1
WBC-GRANULOCYTES (GATING MARKER: CD15)			
FLAER and CD24/CD55 deficiency	15.38	%	<1

Impression:
Flow cytometric analysis shows a PNH clone within RBCs (16.85%), granulocytes (15.38%) and monocytes (75.47%). These findings favour a diagnosis of PNH. Clinical correlation is essential.

Flowcytometry Report

DISCUSSION

The above reported case was of recurrent/chronic pancytopenia with hypercellular marrow with megaloblastic changes which remained unresponsive to Iron/B12/folate therapy and required repeated blood transfusions. The serum bilirubin was normal. There was no evidence of hemoglobinuria or intravascular hemolysis. No organomegaly was observed. The reticulocyte values were slightly increased but RTI was below 2.

The following findings were peculiar in this case:
1. Absence of hemoglobinuria
2. No signs of hemolytic process
3. Pronounced pancytopenia with hypercellular megaloblastic marrow.

It is known that classic PNH present as intravascular hemolytic anemia, while 25% cases may present as aplastic anemia and pancytopenia (but marrow is found to be hypocellular in this presentation) but our case had a clinical scenario which is atypical for PNH.

PNH, although well studied but a rarely encountered cause of anemia should be considered as differential diagnosis in case of hemolytic anemia, refractory or recurrent anemia, as well as pancytopenia (both hypocellular and hypercellular marrow), when possible common causes have been ruled out.

From the standpoint of therapy, it is of utmost importance to find the cause and true nature of anemia. Sadly for PNH, there are very limited options available for treatment which include –HSCT and anti-C5 monoclonal antibody. But in developing countries like India, this treatment is beyond the reach of most of the patients.

CONCLUSION:

In resource poor settings, the disease remain undiagnosed in majority of cases and even if diagnosed, cost and availability of treatment are major distressing factors.

Further research needs to be done to develop more affordable and easily available treatment for the condition.

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