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Case Report

Paroxysmal nocturnal haemoglobinuria - a rare entity in pancytopenia: a case report

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematologic disorder characterized by hemolysis, bone marrow failure, and thrombosis. This case report details a 22-year-old male diagnosed with subclinical PNH, who presented with symptoms of fatigue and dyspnea on exertion. The classical symptoms of hemoglobinuria were not seen in our patient. Laboratory evaluation revealed pancytopenia, macrocytosis and low reticulocyte count. Serum B12 levels and iron studies were normal. Flow cytometry identified deficient expression of glycosylphosphatidylinositol (GPI)-anchored proteins on the patient's erythrocytes, confirming the diagnosis of PNH. As our patient was in the subclinical stage, he responded to conservative therapy. Avoidance of stressors lead to significant clinical improvement. This case highlights the importance of considering PNH in young adults with unexplained pancytopenia, hemolysis, hematuria or venous thrombosis and provides insights into the management of this challenging condition. Financial constraints to the use of eculizumab in PNH, in developing countries like India, may present as a therapeutic challenge. However, response to bone marrow transplantation underscores its efficacy in controlling hemolysis and improving quality of life in PNH patients who develop aplastic anemia.

Keywords: PNH, Pancytopenia, Intravascular hemolysis, Hemoglobinuria, Aplastic anemia

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare debilitating clonal stem cell disorder caused by an acquired mutation of the (PIG)-A gene of the pluripotent hematopoietic stem cell, leading to a deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on the surface of red blood cells, including complement regulators CD55 and CD59. These red blood cells are highly vulnerable to complement activation with the formation of membrane attack complex (MAC).

This results in chronic intravascular hemolysis, pancytopenia and a distinct tendency to venous thrombosis. Variable degree of bone marrow hypoplasia is detected as observed in our case.[1]

CASE REPORT

A 22-year non-comorbid male presented with the generalized fatigue for six months and dyspnea (MMRC grade 2) since last 15 days. Patient was evaluated and routine investigations were sent. Initial lab studies showed severe anemia (Hb=6.4 g/dl), thrombocytopenia (platelet count=20,000) and leukopenia (TLC=3800). Anemia work up showed macrocytosis (MCV=104 fl), low reticulocyte count (0.6% corrected), normal serum LDH and normal serum iron and B12 levels. Patient was subjected to bone marrow aspiration and biopsy which revealed hypocellularity. Although no episode of hematuria was reported in the patient's history, patient was evaluated for PNH with immunophenotyping. Patient was managed with supportive treatment and discharged with advice of regular follow up and avoidance of stressful activities.

Table 1: The immunophenotypic analysis report of our patient, which is diagnostic of subclinical PNH (source: the data has been taken from the hospital records).

Cell type	Deficiency	Results (%)
RBC	PNH clone size (type II and type III combined)	0.27
WBC (monocytes)	FLAER /CD14 deficiency	2.37
WBC (granulocytes)	FLAER /CD16 /CD24 deficiency	2.57

DISCUSSION

PNH is a rare disease with a prevalence of 1-10 cases per million, most commonly involving the young adults. The onset of PNH is insidious and the patient presents with symptoms of either anemia and/or hemoglobinuria. PNH in its early stages of development may present with pancytopenia and constitutional symptoms without dramatic paroxysms of hemoglobinuria, as observed in our patient. However, in 25 percent of patients, the disease may commence as aplastic anemia, for which bone marrow transplant is curative. Patients usually have a propensity for nocturnal hemoglobinuria, especially in the presence of stressors like infection, trauma, surgery, pregnancy, exercise, vaccination, menstruation, blood transfusion and the administration of drugs.[2]

The diagnosis of PNH is confirmed with flow cytometry/immunophenotyping by detecting the absence of GPI-anchored proteins on ≥2 lineages with a reagent known as fluorescent aerolysin (FLAER). The diagnosis of subclinical PNH is made if the percentage of abnormal granulocytes is between 0.05% and 5%. Clinical PNH is diagnosed if the clone is larger.[3]

Table 2: International PNH interest group classification of PNH.[3]

Classical PNH	Hemolysis and thrombosis
PNH in the context of other primary bone marrow disorders	Aplastic anemia or myelodysplastic syndrome
Subclinical PNH	Small PNH clones, but no clinical or laboratory evidence of hemolysis or thrombosis

The degree of anemia may vary depending upon the severity intravascular hemolysis and relative bone marrow hypofunction. With ongoing intravascular hemolysis, the reticulocyte count is elevated, haptoglobin markedly reduced along with an elevation of the serum LDH. But hypocellular stage shows reduced reticulocyte count. Because of the cytopenias, patients may be misdiagnosed as having either a myelodysplastic syndrome or aplastic anemia.[4]

Unusual modes of presentation, as seen in our patient, that is pancytopenia with hypocellular marrow may cause diagnostic dilemma in patients. However, diagnosis should be sought in any patient with a refractory anemia, either hypercellular marrow with normal serum iron and B12 studies, or in non-spherocytic, direct Coomb's -negative intravascular hemolysis. Ham's acid serum test and sucrose haemolysis test were the diagnostic tests for PNH used in the past based on the principle of complement mediated hemolysis. However, these tests are obsolete now, and have been replaced with immunophenotyping.[5]

Complications of PNH include hemoglobinuria, which may present as acute renal failure. Long term hemoglobinuria may result in acquired Fanconi's syndrome. Hemolytic episodes can accompany esophageal spasm and erectile dysfunction. Thrombosis can occur in twenty percent of cases involving the hepatic veins (Budd-Chiari syndrome) and the portal, cerebral or the extremity veins. Splenic enlargement may occur due to venous obstruction by thrombosis. However, arterial thrombosis is rare.[6]

End-organ damage can occur in PNH, including renal tubular damage and raised pulmonary pressures, which is caused by subclinical micro-thrombi and the deposition of iron due to chronic hemolysis. Thus, without treatment, hemolysis in PNH can cause iron deficiency, thrombosis, and end-organ damage which includes chronic renal failure and pulmonary hypertension.[7]

Treatment

Treatment of subclinical cases is mainly supportive with avoidance of the precipitating stressors. Many patients are dependent on chronic blood transfusions which poses a risk for iron overload. A trial of therapy with oxymetholone and androgen therapy such as Danazol, may help with anemia. Use of prednisone is restricted for severe exacerbation of hemolysis.[8] Soliris (eculizumab), the first C5-complement inhibitor was approved by FDA in 2007, which acts by blocking the terminal complement pathway. However, the use is limited due to its cost constraints. In 2018, FDA also approved Ultomiris (Ravulizumab) for the treatment of the hemolysis in PNH. After unknown consequences and insufficiencies of terminal complement inhibition were identified, the first proximal complement inhibitor Pegcetacoplan was introduced in 2021.[9]

Recently, in 2024 Epysqli, a Soliris biosimilar, has also been introduced which has reduced cost. However, patients with aplastic anemia and small PNH clones are more likely to respond to immunosuppressive treatment Granulocytopenia and/or thrombocytopenia (in the absence of splenomegaly or thrombosis) may be treated with anti-thymocyte globulin and/or other immunosuppressants such as cyclosporine.[10]

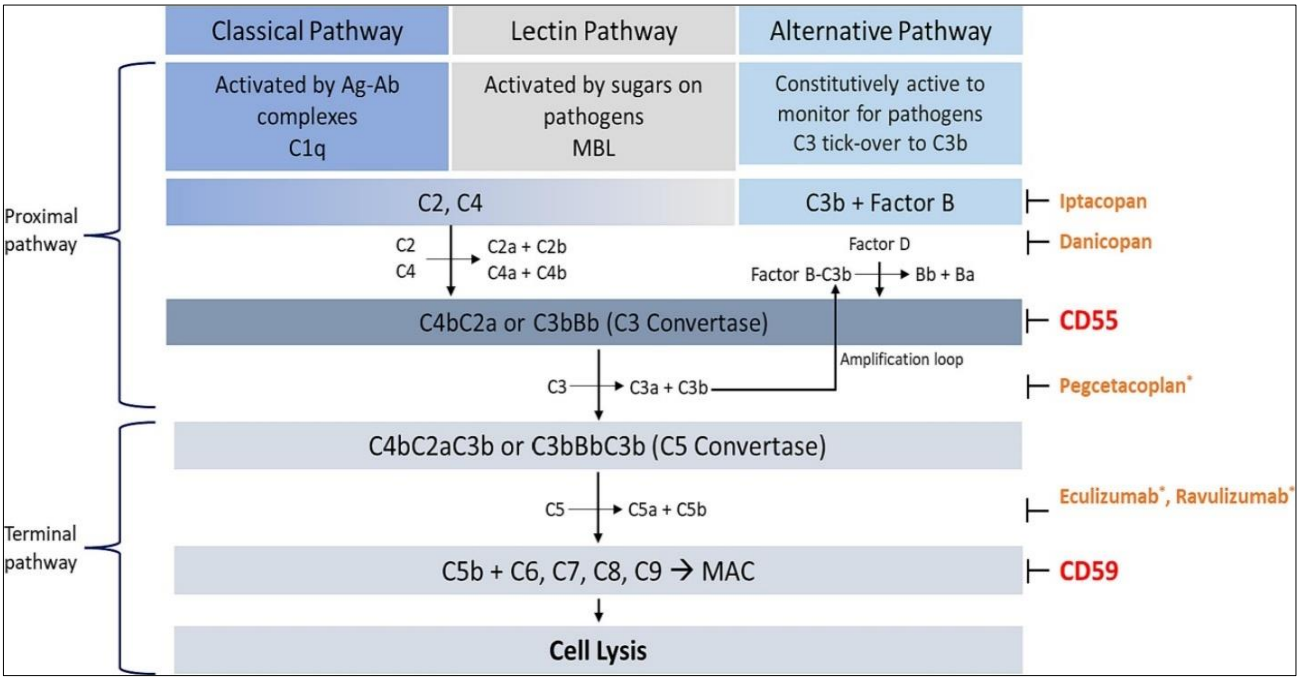

Figure 1: Pathophysiology of hemolysis via complement cascade and target of complement inhibition by the drugs used in treatment.[7]

CONCLUSION

PNH is a rare clinical entity which must be considered in young patients especially males, who present with pancytopenia, in the absence of nutritional causes. Patients may present with anemia or hemoglobinuria in the initial stages, and later may develop aplastic anemia. Thus, all the patients should be evaluated with flow cytometry to identify the underlying cause. Subclinical PNH, as seen in our patient, may respond to avoidance of stressful activities. However, definitive therapy for PNH is complement inhibition and for aplastic anemia is bone marrow transplant.

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