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A RARE HEMATOLOGICAL MANIFESTATION OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA(PNH) WITH PANCYTOPENIA IN A YOUNG MALE PATIENT

General Medicine

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder that can cause severe complications like hemolytic anemia, bone marrow failure, and blood clots.[1] It occurs due to a mutation in the PIG-A gene,on chromosome Xp22.1, leading to the absence of protective proteins CD55 and CD59 on red blood cells.[3] Without these proteins, the cells are vulnerable to the body's complement-mediated lysis. We encountered a 25-year-old man who presented with nasal, gum, and rectal bleeding, fatigue, breathlessness, and fever. His blood tests revealed severe pancytopenia, and a bone marrow biopsy showed aplasia. Flow cytometry confirmed CD55 deficiency, diagnosing him with PNH. He was treated with blood and platelet transfusions and antibiotics, and his condition improved. He was advised to consider a bone marrow transplant for long-term management. Apart from causing anemia and other symptoms, PNH can also cause life-threatening blood clots due to free hemoglobin disrupting nitric oxide levels, leading to vessel damage,making venous thrombosis a major cause of death. Treatment often includes eculizumab, which reduces hemolysis and clot risks, but it is costly and less effective in severe bone marrow failure.[7] In such cases, stem cell transplantation is the only curative option. Early diagnosis in patients with unexplained anemia or pancytopenia is essential for timely and effective treatment.

KEYWORDS

Paroxysmal nocturnal hemoglobinuria, Pancytopenia, Intravascular hemolysis, Stem cell transplantation

INTRODUCTION:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disease that manifests as hemolytic anemia, bone marrow failure, smooth muscle dystonia and thrombosis.[1] It is an acquired defect of the glycosylphosphatidylinositol associated proteins CD55 and CD59.[1] These protein deficiencies lead to complement- mediated cell lysis and other clinical manifestations. Flow cytometry analysis of antibodies directed against CD55 and CD59 is the gold standard technique for the diagnosis.[2,3,4] PNH originates from a multipotent hematopoietic stem cell that acquires a mutation in a gene called phosphatidylinositol glycan anchor biosynthesis, class A (PIG-A) located on chromosome Xp22.1. This leads to partial or absolute deficiency of all 'glycophosphatidyl-inositol-anchor proteins' (GPI-AP).[6,7] These proteins serve different functions like enzymes, receptors; complement regulators and adhesion molecules. The protein deficiencies such as CD55 (decay accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL) lead to complement mediated cell lysis and other clinical manifestations.[1]

CASE PRESENTATION:

A 25 year old male patient, not a known case of any major medical illness came with complaints of nasal bleed, gum bleed and per rectal bleeds since 1 month which increased over 1 week. The patient also complained of breathlessness which increased on exertion and easy fatigability with fever for past 5 days. There is no history of abdominal pain,haematemesis,abdominal distention, pedal edema , jaundice.

On general examination, the patient had tachycardia, pallor present. No jaundice, no hepatosplenomegaly.

On per rectal examination no obvious abnormality was found but patient complained of Blood in urine that is Haematuria.

INVESTIGATIONS AND FINDINGS :

The table below shows the result of the Complete Blood Count :

Hemoglobin(gm/dl)	6.10
WBC(per cmm)	2000
PC(per cmm)	12000
MCV(fl)	76
MCH(pg)	24.50
Reticulocyte count(%)	0.5
Immature platelet fraction(%)	0.9

Then, bone marrow biopsy was done which revealed aplastic marrow.

On further investigations for the cause of aplastic anemia, the patient tested positive for CD55 deficiency on flow cytometry. Also many other laboratory investigations were conducted to rule out Dengue - NS1 Antigen test, Malaria - Rapid diagnostic test, and HHH, all of which returned as negative results. Additionally, Vitamin B12 levels were within the normal range that is around 13.5mg/dl, eliminating the possibility of megaloblastic anemia.

MANAGEMENT AND OUTCOME:

With the characteristic features and considering the final diagnosis of PNH with aplasia, patient was started with multiple packed cell volume transfusions. And also, platelet transfusions with symptomatic treatment of other antibiotics were given. After which the patient's haemoglobin count and platelet count improved.

Studies also reveal that patients with bone marrow aplasia associated with PNH are less likely to respond to eculizumab, seen that the main mechanism of anemia, in these cases, is bone marrow suppression, instead of complement-mediated hemolysis.[7] Also, financial constraints prevented the patient from pursuing this therapy. So, the patient was discharged after counselling him and his relatives for bone marrow transplantation for further long-term management.

DISCUSSION:

We report a case of a young male patient who presented with nasal,gum and per rectal bleeding for one month. The patient also complained of breathlessness which increased on exertion and early fatigability than in the usual days. Diagnosis of PNH was confirmed by typical clinical features and flow cytometry.

In PNH there is complement induced lysis of RBCs due to abnormal sensitivity of RBC cell membrane. This is due to acquired defect in the gene for phosphatidylinositol class A(PIG-A) thereby causing a deficiency of glycophosphatidylinositol(GPI) which is a sheet anchor for RBC cell membrane proteins CD55 and CD59, complement regulatory proteins which block intravascular and extravascular hemolysis respectively in normal humans, are deficient in PNH. Hemolysis occurs in PNH because these patients RBCs lack GPI

anchor which is required to attach CD55 and CD59 to surface of the RBC. This permits unregulated hemolysis.The next feature is the thrombosis which is the leading cause of death in patients with PNH. The pathogenesis causing thrombosis is not completely understood but hypothesized to be due to free hemoglobin released from hemolysis of RBC which attracts nitric oxide which induces vasoconstriction and damages the vascular endothelium forming a nidus for thrombus formation. Venous thrombosis often occurs in location such as hepatic, portal,mesenteric ,dermal and cerebral veins.

A minority of patients develop pancytopenia due to bone marrow disorders like aplastic anemia or primary myelofibrosis. PNH is classified into classic PNH (presence of hemolysis with no marrow abnormality), PNH with marrow disorders(aplastic anemia/myelodysplastic syndrome (MDS)/primary myelofibrosis (PMF) and subclinical PNH-without clinical evidence.[1]

Also, the diagnosis of PNH can be suspected when we come across a case of coombs negative hemolytic anemia or aplasia.

The most advanced and effective treatment for PNH is Stem cell transplantation and competent inhibition with eculizumab.[6] Eculizumab is also a lifesaving therapy that is associated with a greater than 50% reduction in transfusion requirements and a close to 70% reduction in risk of thrombotic events and adverse vascular complications.

Eculizumab and anticoagulation therapy is much more effective but allogenic stem cell transplantation is advised with severe pancytopenia as every patient might not be able to afford eculizumab & ACT therapy ; And studies have revealed that patient with cytopenia or aplasia are less likely to respond with eculizumab, as it's seen that the mechanism of anemia is bone marrow suppression, instead of complement mediated hemolysis.[7]

CONCLUSION:

In the presentation, a young man who presented to us with Pancytopenia and history of bleeding was found to have coombs negative hemolytic anemia. But there was no history of jaundice and was not at a severe stage of multiple vein thrombosis. So, in such complex and confusing cases we must suspect one of the differential diagnosis as paroxysmal nocturnal hemoglobinuria (PNH). And in PNH, the recommended and gold standard treatment is stem cell transplantation which should be affordable to the patient.

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