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A CASE REPORT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Haematology

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ABSTRACT

Paroxysmal Nocturnal Hemoglobinuria with aplastic anemia is an under-recognized cause of bone marrow failure. We present a case of a 20-year-old male patient who presented to us with severe anemia along with pancytopenia. This is a unique case since the patient's bone marrow biopsy revealed an aplastic picture yet the patient had palpable splenomegaly along with icterus and severe and persistent headaches which could not be explained by aplastic anemia alone. So we investigated the case further to finally reach the diagnosis of Paroxysmal Nocturnal Hemoglobinuria.

KEYWORDS

Paroxysmal Nocturnal Hemoglobinuria, Pancytopenia, Aplastic Anemia, Eculizumab, flow cytometry, Bone Marrow Transplant,Triple Immunosuppressive therapy

INTRODUCTION

Paroxysmal Nocturnal Hemoglobinuria is an acquired cause of intravascular hemolysis. It is caused due to a defect in terminal complement pathway inhibitors named Decay Accelerating Factor(CD-55) and Membrane Inhibitor of Reactive Lysis/MIRL(CD-59). It is caused due to a defect of the PIGA(Phosphatidyl Inositol Glycoprotein-A) gene which encodes for the terminal complement pathway inhibitors DAF and MIRL. Patients with PNH classically present with a triad of Intravascular Hemolysis, Pancytopenia, and Thrombosis. Diagnosis of PNH is usually confirmed by Flow Cytometry of blood granulocytes and FLAER assays for CD-55 and CD-59. In recent years the evolution of treatment strategies like hemopoietic stem cell transplantation and complement inhibition with eculizumab though very costly have proven to be highly effective[1]. The disease manifests itself in two main clinical pictures: hemolytic and hypoplastic type. Chronic intravascular hemolysis findings are typically more prominent in the hemolytic type, whereas pancytopenia is typically more prominent in the hypoplastic type. Coombs-negative hemolytic anemia, the presence of thrombosis, iron deficiency, and pancytopenia should prompt PNH examination. PNH can be found alone (classical PNH) or accompanied by aplastic anemia and myelodysplastic syndrome (MDS) [2]. PNH also has clinical importance in terms of hematological malignancies with which it can be seen. The presence of a PNH clone with MDS and aplastic anemia changes the treatment approach completely. Similarly, because of being a clonal stem cell disease, it also possesses risk for the transformation of acute myeloid leukemia. This rate is 1% within publications [3]. In the series reported by Wang *et al.*, 35% of patients with refractory anemia had a PNH clone and 20% of 5q-syndrome patients also developed a PNH clone during the follow-up period. However, deficiency of multiple glucose phosphate isomerase-linked (GPI-linked) proteins in granulocytes were not detected in patients with a diagnosis of sideroblastic anemia, refractory anemia with an excessive blast, or clear acute myeloid leukemia. In general, it can be stated that acute leukemia transformation is seen less frequently and the prognosis is better for MDS cases with a PNH clone; however, there is no difference at the point of treatment [4].

Case Study

A 24-year-old male patient presented to our hospital with the chief complaint of generalized weakness for the last 5 days. He also complained of passing red-colored urine for the last 7 days. Alongside he complained of fever with chills for the last 7 days. He complained of inability to work and extreme fatigability on minimal exertion. The patient also complained of severe but episodic headache for the last 15 days. The patient had no complaints of vomiting, chest pain, abdominal pain, breathlessness, altered sensorium, or neck rigidity. The patient had a significant history of multiple blood transfusions and Platelet Rich Plasma (PRP) transfusions. In December 2018 patient underwent a bone marrow biopsy at a peripheral hospital which showed hypocellular bone marrow with decreased cells of all 3 lineages suggestive of aplastic anemia. Following this bone marrow biopsy report patient went to a tertiary care hospital where he was counselled for a bone marrow transplant. No further investigations were done at that time to find out the cause of aplastic anemia. The patient's HLA matching was done and his closest match was his father, who matched 3/6 with him. So the patient couldn't get a bone marrow transplant. So, he was counselled for triple immunosuppressive therapy using ATG (Anti Thymocyte Globulin), Cyclosporine, and Danazol. The patient underwent 3 cycles of triple immunosuppressive therapy which failed to show any significant improvement in the patient's condition. Since then the patient has been on 2 pints of PCV and 4 pints of PRP(Platelet Rich Plasma) every month. Following this long course patient presented to our hospital in July 2022 with complaints of generalized weakness, passing red-colored urine, and fever.

On examination-Patient had severe pallor and visible mild icterus seen on the conjunctiva. His on-admission vitals were heart rate of 96/min, Blood pressure of 124/70 mmHg, and oxygen saturation of 99% on room air. His Central Nervous System examination revealed that he was conscious and oriented to time, place, and person. Although he had a headache he did not have neck rigidity or Kernig's or Brudzinki's sign. His Cardiovascular System examination and Respiratory System examination revealed no significant abnormalities. His per abdomen examination revealed palpable splenomegaly up to 2 fingers width. He had no hepatomegaly. His both pupils were equally reactive to light. His both planters were flexors. The patient was well-built and in a healthy mood.

Investigations

On admission routine workup:

Hemoglobin	6.8 gm/dl
RBC count	3.5 million/dl
WBC count	4900 /dl
Polymorphs	50%
Lymphocytes	44%
Monocytes	05%
Eosinophils	01%
Platelet Count	12000 /dl
S.Urea	41 mg/dl
S. Creatinine	1.22 mg/dl
S. Total Bilirubin	7.2 mg/dl
S. Direct Bilirubin	3.1 mg/dl
S. Indirect Bilirubin	4.1 mg/dl
S. Sodium	135 mEq/L
S. Potassium	4.3 mEq/L
S. SGPT	497 IU/L

S. SGOT	370 IU/L
S. ALP	197 IU/L
S. LDH	1761 U/L
S. Ferritin	4927 ng/ml
S. Iron	230.26 mcg/dl
S. TIBC	319.96 mcg/dl
S. Percentage Saturation of Transferrin	71.97 %

The patient's iron profile revealed a picture of iron overload which is most likely due to multiple blood transfusions.

Test Name	Results	Units	Bio. Ref. Interval
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) (Flow Cytometry)			
RBCs-RED BLOOD CELLS (GATING MARKER: CD235a)**			
Type II (Partial CD59 deficiency)**	0.31	%	<1
Type III (Complete CD59 deficiency)**	**6.36**	%	<1
Type II & Type III (Combined deficiency)**	**6.97**	%	<1
WBC-MONOCYTES (GATING MARKER: CD33/CD64)*			
FLAER, CD14 and CD55 deficiency**	**91.46**	%	<1
WBC-GRANULOCYTES (GATING MARKER: CD15)*			
FLAER and CD24/CD55 deficiency**	**86.80**	%	<1

Flow Cytometry Report-

Flow cytometry analysis shows a PNH clone within RBCs (6.97%), granulocytes (86.8%), and monocytes (91.46%).

Bone Marrow Examination Report of 2018-

Bone Marrow is Hypocellular for age with a predominance of fat spaces and reduced trilineage hemopoiesis. Erythroid series is decreased in nature with an almost complete absence of mature granulocyte forms. The Myeloid series is markedly decreased in nature. Megakaryocytes are decreased in number.

Bone Marrow Examination Report of 2022 (After admission to our hospital)-

Cellularity- Moderately Hypocellular at 40-50%
Erythroids-Present, mildly increased, and normoblastic in maturation.
Myeloids- Present, reduced, and normal in maturation.
Megakaryocytes- Present and markedly reduced.

Bone Marrow Examination revealed an increase in hemosiderin-laden macrophages and hypoplastic marrow. This report reveals a picture of iron overload most likely due to multiple blood transfusions. Imaging Studies like NCCT Head and CT Venography Brain were unremarkable**.**

Treatment

The patient was given a total of 6 pints of PCV and 4 pints of Platelet Rich Plasma(PRP) during the entire course of his treatment at our hospital. Due to financial issues patient could not afford Eculizumab therapy. Since the patient's closest HLA match was his father(3/6), which was inadequate for Allogenic Bone Marrow Transplant so it could not be done. So patient was given Immunosuppressive therapy in form of Tab Cyclosporine 100mg BD which showed improvement in his cell counts. Along with this patient was given supportive management for fever and nutritional supportive medications.

The patient was discharged on Tab Cyclosporine 100 mg BD for immunosuppresion and Tab Deferasirox(5mg) for the management of iron overload caused by multiple blood transfusions.

DISCUSSION

We report a 24-year-old male patient who presented with fever, red-colored urine, weakness, headache, and jaundice. Diagnosis of PNH was confirmed by typical clinical features and flow cytometry. The cause of headache remains undiagnosed but one hypothesis could be episodic microthrombi in cerebral vessels which could not be appreciated on CT Venography Brain. It could be further investigated with MR Venography Brain.

In PNH there is complement-induced lysis of RBCs due to the abnormal sensitivity of the RBC cell membrane. This is due to an acquired defect in the gene for phosphatidylinositol class A (PIG-A) thereby causing a deficiency of glycosylphosphatidylinositol (GPI) which is a sheet anchor for cell membrane proteins [5]. CD55 and CD59, complement regulatory proteins which block intravascular and extravascular hemolysis respectively in normal humans, are deficient in PNH [6]. Hemolysis occurs in PNH because these patients' RBCs lack the GPI anchor which is required to attach CD55 and CD59 to the surface of the RBC. This permits the unregulated formation of certain complement attack complexes which damages the RBC membrane resulting in intravascular hemolysis. This causes a reduction in hemoglobin and hemoglobinuria with a resultant increase in LDH. The next feature is thrombosis which is the leading cause of death in patients with PNH. The pathogenesis causing thrombosis is not completely understood but is 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. Also, platelets release procoagulant particles during complement-induced hemolysis, which facilitates thrombosis. Thrombosis involves the venous rather than the arterial system. Venous thrombosis often occurs in locations such as hepatic, portal, mesenteric, dermal, and cerebral veins [7]. A minority of patients develop pancytopenia due to bone marrow disorders like aplastic anemia or primary myelofibrosis.

As mentioned, the pathology is based on CD55 and CD59 deficiency. However, CD55 and CD59 deficiency can also be seen in autoimmune thrombocytopenia, hemolytic anemia, and systemic lupus erythematosus. It is possible to define them as diseases that create a 'PNH-like phenomenon' [8, 9].

CONCLUSION

The presence of aplastic features in a patient with hypocellular bone marrow along with clinical features of severe weakness, reddish discoloration of urine, and headache in a young patient should prompt a diagnosis of PNH. Flow cytometry findings of CD-55 and CD-59 deficiency confirms the diagnosis of Paroxysmal Nocturnal Hemoglobinuria. Treatment options remain limited to Bone Marrow Transplantation and monoclonal antibodies like Eculizumab.

REFERENCES

[1] http://www.ijcasereportsandimages.com/archive/2015/006-2015-ijcri/CR-10525-06-2015-seetharaman/ijcri-1052506201525-seetharaman-full-text.php
[2] Illingworth A, Marinov I, Sutherland DR, Wagner-Ballon O, DelVecchio L. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 3 - data analysis, reporting and case studies. Cytometry B Clin. Cytom. 94(1), 49–66 (2018). Guidelines state that paroxysmal nocturnal hemoglobinuria can be found alone (classical paroxysmal nocturnal hemoglobinuria) or accompanied by aplastic anemia and myelodysplastic syndrome. Crossref, Medline, Google Scholar
[3] Ruiz-Argüelles A, Llorente L. The role of complement regulatory proteins (CD55 and CD59) in the pathogenesis of autoimmune hemocytopenias. Autoimmun. Rev. 6(3), 155–161 (2007). Presence of paroxysmal nocturnal hemoglobinuria clone with myelodysplastic syndrome and aplastic anemia changes the treatment approach completely. Similarly, because of being a clonal stem cell disease, it also poses risk for the transformation of acute myeloid leukemia. This rate is 1% within publications. Crossref, Medline, Google Scholar
[4] https://www.futuremedicine.com/doi/10.2217/ijh-2020-0013
[5] Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood 2014 Oct 30;124(18): 2804–11
[6] Pu JJ, Brodsky RA. Paroxysmal nocturnal hemoglobinuria from bench to bedside. Clin Transl Sci 2011 Jun;4(3):219–24.
[7] Hill A, Kelly RJ, Hilman P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood 2013 Jun 20;121(25):4985–96.
[8] Nakamura N, Sugawara T, Shirato K, et al. Paroxysmal nocturnal hemoglobinuria in systemic lupus erythematosus: a case report. J. Med. Case Rep. 5, 550 (2011). CD55 and CD59 deficiency can also be seen in autoimmune thrombocytopenia, hemolytic anemia, and systemic lupus erythematosus. It is possible to define them as diseases that create a 'paroxysmal nocturnal hemoglobinuria-like phenomenon'.Crossref, Medline, Google Scholar
[9] Luzzatto L, Gianfaldoni G. Recent advances in biological and clinical aspects of paroxysmal nocturnal hemoglobinuria. Int. J. Hematol. 84(2), 104–112 (2006). Crossref, Medline, CAS, Google Scholar