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PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA- A RARE HAEMOLYTIC ANAEMIA

Medicine

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ABSTRACT

Introduction: Paroxysmal Nocturnal Haemoglobinuria (PNH) is rare type of haemolytic anemia characterized by Intravascular Haemolysis, Venous Thrombosis and may be associated with Aplastic Anaemia. Current case report presents a case of Paroxysmal Nocturnal Haemoglobinuria. **Case presentation:** 19-year male presented with complains of red coloured urine on/off, mild abdominal pain for 1 month, fever with chills, vomiting for 7 days, oliguria for 3 days. Bone Marrow Biopsy done I/V/O persistent pancytopenia even after resolving of Acute Febrile Illness which was suggestive of Cellular Marrow with Trilineage Haematopoiesis-yet Hypoplastic bone marrow, Blasts <5%, no evidence of granuloma, malignancy. **Conclusion:** PNH may go undiagnosed for variable time period due to variable clinical presentation which causes delay in early treatment before development of complications. Furthermore, it may be underdiagnosed illness with true incidence and prevalence still not known since increasingly being identified.

KEYWORDS

Paroxysmal Nocturnal Haemoglobinuria, haemolytic anemia, pancytopenia

INTRODUCTION:

Paroxysmal Nocturnal Haemoglobinuria (PNH) first described in 1882[1] is characterized by Intravascular Haemolysis, Venous Thrombosis and may be associated with Aplastic Anemia.[2] The characteristic symptom of PNH- Abdominal pain, Dysphagia, Erectile failure and intense lethargy can be attributed to intense Intravascular Haemolysis and release of free Haemoglobin from its intracellular compartment.[3] which also causes deficiency of nitric oxide. PNH arises via somatic mutation in Phosphatidyl Inositol Glycan complementation class A gene (PIG-A) in hematopoietic stem cell followed by subsequent expansion of this abnormal clone.[4]Loss of GPI linked complement inhibitors, CD55 and CD59, on red blood cells leads to chronic and/or paroxysmal intravascular haemolysis and a propensity for thrombosis, organ dysfunction, and hypocellular or dysplastic bone marrow.

PNH is a chronic condition frequently affecting young individuals. Symptoms are due to ongoing haemolysis and or insufficient haematopoiesis. Patients have acute exacerbations of haemolysis on background of persistent lower level of haemolysis. Anaemia and the need of transfusion to sustain HB levels occur frequently. The most dangerous complication of PNH is Venous Thrombosis which occurs in 50% of patients with haemolytic disease and is cause of death in at least one third of patients.[2,4,5-11]. Its incidence and prevalence are poorly defined.[12,13] Unknown frequency worldwide with little information on Incidence. Figures of incidence quoted by PNH information Website ranges between 1 per 100,000 to 5 per 10,000,00 population.[14,15,16] Diagnosis of PNH may be delayed because of its non-specific clinical features, variable clinical presentation, and rarity. Early and accurate diagnosis is particularly important since effective complement inhibitors have become available.

Case Report:

We presented case of 19-year male who got first time admitted in our hospital on 26-10-2019 with complains of red coloured urine on/off, mild abdominal pain for 1 month, fever with chills, vomiting for 7 days, oliguria for 3 days. Patient baseline reports were available suggestive of Pancytopenia (Hemoglobin-7.8, Total Leukocyte Count-2690, Platelet-68000) with Acute Kidney Injury (AKI) (Serum Creatinine -11.18). Fever profile-Dengue IgM Positive. Since patient was hemodynamically unstable, was admitted in ICU and started on Inotropes. 5 sessions of Dialysis were given in view of oliguria and AKI.DIC profile was done which was negative. Serum B12 level were done I/V/O Pancytopenia-came to be within normal range (233). Total bilirubin-Within Normal Range. Serum iron profile was within normal limits. Retic count was done which was low. Viral markers-Non reactive. Bone Marrow Biopsy done I/V/O persistent pancytopenia even after resolving of Acute Febrile Illness which was suggestive of Cellular Marrow with Trilineage Haematopoiesis-yet Hypoplastic bone marrow, Blasts <5%, no evidence of granuloma, malignancy. 2 Unit PCV transfused I/V/O low Hb-Probable diagnosis of post viral suppression of bone marrow was made and patient continued on haematinics. Gradually platelet counts, haemoglobin improved, hence patient was discharged on haematinics. Patient continued to follow up in Haematology OPD.

Reports-

INVESTIGATIONS	26/10	30/10	4/11	7/11	11/11	12/11	13/11
Haemoglobin (g/dl	6.7	7.2	6.8	7.3	7.6	7.2	7.3
Total leukocyte count (1000/µl)	3.3	3.0	4.5	2.7	3.6	3.5	5.2
Platelets(1000/µl)	66	46	48	52	90	69	82
Total Bilirubin (mg/dl)	1.3	0.9	0.4	0.3	0.34		
SGOT/SGPT	31/10	35/08	36/10	32/12			
Retic %	2	1.8					
LDH	909						
S. creatinine	9.74			1.9			1.1

USG A+P-Raised kidney echogenicity
Serum Fibrinogen-24.09, PT-13.50, INR-1.18
Serum Iron-96.3, % Transferrin saturation-27.7%.,
Ferritin-258.3
Serum B12-233.60
Retic-2.0%
Bone Marrow Aspirate – Cellular marrow with trilineage Haematopoiesis with mild hem phagocytosis.
Bone Marrow Biopsy-Hypoplastic Marrow.
Urine R/M- 6-7 RBCs / HPF
Fever Profile – Dengue IgG/IgM positive

Patient again presented to our casualty on 26-08-2022 approximately after 2 years with complains of giddiness, dyspnoea on exertion Grade2, generalized weakness, red coloured urine on/off which precipitated in night hours, dysphagia, abdominal pain.

No history of fever, no history of similar complains in other family members. On examination- Vitally stable, Pallor+++, Icterus++. Outside investigation: Hb-5.8, TLC-3470, Platelets-222000.So, patient got admitted in Ward. Peripheral smear-Hypochromia (+++), Microcytosis (++). Serum Iron Profile done in view of microcytic, hypochromic anaemia.

Serum Iron-27.33ug/dl (70-180); Percentage Transferrin Saturation-6.18% (13-45); Total Iron Binding Capacity-442.00 µg/dl (250-400).Thus a probable diagnosis of Iron deficiency anaemia was made.

However, I/V/O raised Total Bilirubin/Indirect bilirubin-6.8/5.8. a differential of Haemolytic Anaemia was considered and work up for haemolytic anaemia done. LDH-2809(Raised), Corrected Retic-3.1%. Serum B12->2000.

USG A+P-Mild hepatomegaly, no splenomegaly.

ANA- Negative, DCT/ICT-Negative. High Performance Liquid Chromatography- Normal differential Hb percentage, G6PD- Not deficient. In absence of splenomegaly, and LDH value Approx > 5 times of normal range with indirect bilirubinemia, we considered it as Predominant Intravascular Haemolysis. Serum Haptoglobin-<0.07g/L (0.3-2.0)-(NOTE-This value of haptoglobin was got after 3 consecutive blood samples; since technician repeated samples as samples got haemolysed soon after collection)further supported Intravascular Haemolysis view of history of Red Coloured urine On/Off(especially during night hours),dysphagia, vomiting-Coombs Negative Intravascular Haemolytic Anaemia with Iron Deficiency Anaemia(can be due to loss of haemoglobin and hence Iron in urine)-no history of similar complains in family members(Since PNH is acquired disease and ruling out hereditary haemolytic anemias) -a probable diagnosis of Classical Haemolytic Paroxysmal Nocturnal Haemoglobinuria was thought of (with no evidence of marrow failure).Hence PNH profile(flow cytometry) was sent which revealed-**PNH Clone (CD55/59-Negative) 76.4% of granulocytes (i.e. >50% PNH Clone on granulocytes)-Classical PNH.**

After working out diagnostic dilemma, patient was transfused 2 PCV I/v/o low Hb and started on Haematinics. Serial CBC monitoring showed increasing HB.No evidence of thrombosis in any abdominal or cerebral site found.

For Definitive Management, patient is being worked up for Bone Marrow Transplant and Eculizumab/Rovelizumab trial.

REPORTS:

INVESTIGATIONS	24/08/22	27/08	29/08	1/09
HB	5.2	5.8	7.0(after PCV)	7.4
TLC	3470	4.47	4.21	5.55
PLATELET	222,000	164,000	173,000	158,000
T.BILI/D.BILI	6.5/1.0	6.8/1.0	3.3/0.3	3.7/0.5
SGOT/PT	62/10	77/11	65/10	127/14
S.CREAT	0.85	1.0	1.1	1.6
LDH	2809	2125	2228	2500

PNH Profile-Flowcytometry

Markers	Result	Units
CD55/59Negative	76.4	% of granulocytes
CD55/59Negative	4.1	% of monocytes

Uric Acid-4.4
G6PD-Not Deficient
DCT/ICT-Negative
C3/C4/CRP-77/16/2.0
ANA-Negative
TSH/T3/T4-4.689/124.32/8.37
Retic-6.1 %
Urine R/M – NAD
Serum B12->2000
Serum Iron Profile- Iron: 27.
Total Iron Binding Capacity:442
% Transferrin Saturation:6.18
Fever profile: Negative
USG A+P- Hepatomegaly
Serum Haptoglobin-<0.07%

Cola Color Urine

CONCLUSION:
PNH may go undiagnosed for variable time period due to variable clinical presentation which causes delay in early treatment before development of complications. Furthermore, it may be underdiagnosed illness with true incidence and prevalence still not known since increasingly being identified. In our case, there was no triad finding of PNH, other than haemolytic anaemia. Most likely, this patient was having PNH since 2019 or even before which was precipitated by acute febrile illness and got finally diagnosed in 2022.

Footnotes:
Financial and competing interests' disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research:
A written informed consent was obtained from our patient to share and publish this case presentation.

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