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Case Reports

Paroxysmal Nocturnal Haemoglobinuria - An Atypical Presentation

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Abstract:

Paroxysmal Nocturnal Haemoglobinuria (PNH) is a rare, acquired disorder of haemopoitic stem cell, characterized by abnormal sensitivity of red cells to haemolytic action of complement leading to intravascular haemolysis. Though PNH typically presents as nocturnal haemoglobinuria, however presentation varies as for example bicytopenia, aplastic anaemia or repeated venous thrombosis. One such atypical presentation was seen in 35 years old male who presented with the history of generalized weakness, fever and oral ulceration. The PNH was diagnosed by flow cytometric analysis of GPI linked protein and associated laboratory features of chronic haemolysis. We report this case to create awareness about the fact that PNH can present without haemoglobinuria.

Key words: *Paroxysmal Nocturnal Haemoglobinuria, Presentation, Diagnosis.*

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Introduction:

Paroxysmal Nocturnal Haemoglobinuria (PNH) is a rare form of acquired haemolytic anaemia with a prevalence of 1-5 per million. Both men and women are equally affected. The median age of presentation is 42 years (age range 16-75 years). PNH was first described in 1866 in a patient with bouts of dark coloured urine. Since then, there has been tremendous progress in its diagnosis and management. The major clinical feature of PNH are – heamolytic anaemia, haemoglobinuria, venous thrombosis and deficient haematopoiesis. It has a chronic course with varied presentation. [1,2,3]

Case summary:

A 35 year-old-male, married, non diabetic, normotensive, non smoker, muslim, fisherman, hailing from kuakata, patuakhali was admitted in DMCH on 14th November, 2016 with complaints of Generalized weakness for about 1 month and fever and oral ulceration for about 15 days.

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Patient complained of progressively increasing generalized weakness for about 1 month and he felt extremely tired even after mild activity. He also developed low grade, intermittent fever for 15 days which was not associated with chill or rigor, no evening rise of temperature and subsides spontaneously without sweating. On query patient complained of occasional dry cough. At the same time the patient noticed ulceration on tongue and buccal mucosa, which were painful. But there was no skin rash, arthralgia, photosensitivity, genital ulcer, dysphagia or any dental problem. On query the patient complained of passage of dark coloured urine throughout the day for 15 days. But repeated questioning, he denied about any change of colour of urine after waking up from sleep. There is no history of weight loss, previous jaundice, bony pain, bleeding from any site, contact with TB patient, sexual exposure or exposure to any chemical and he has no significant drug history. Patient had no significant past illness and family history related to this condition.

On examination patient was ill looking, severely anaemic, mildly icteric, no bony tenderness, no palpable lymph node, pulse – 112/min, BP – 110/50 mm Hg, temp. - 99°F, Bed side urine: Dark Orange (No colour change after serial urine sample/after prolong standing), Urine for sugar & protein: Nil.

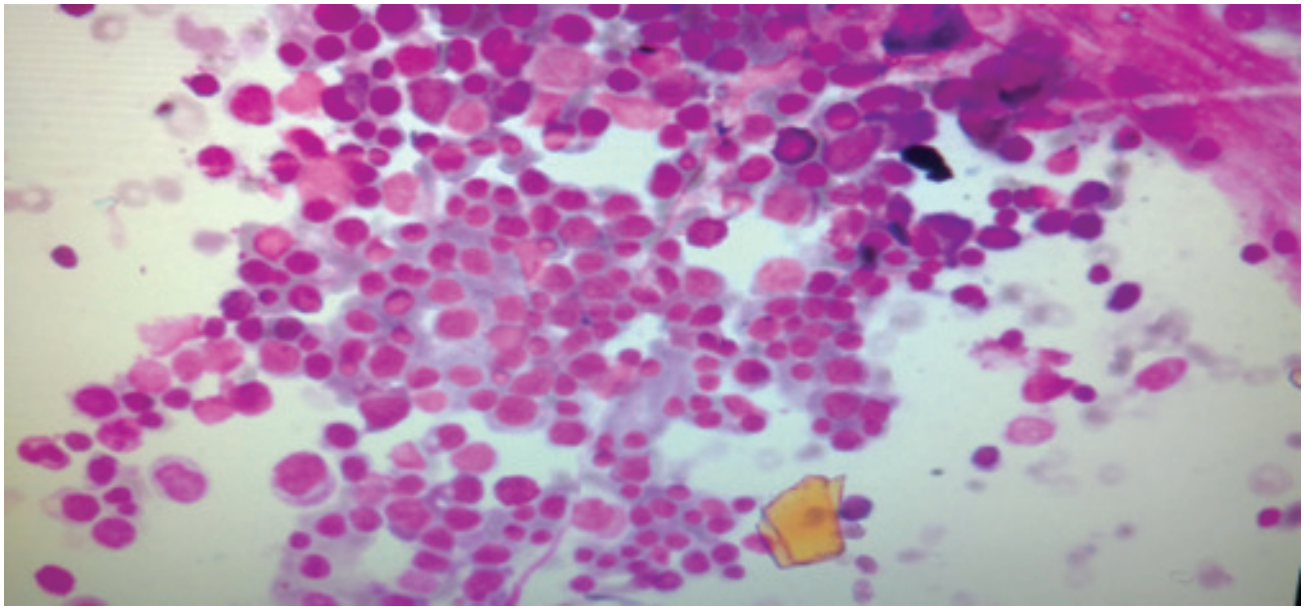

Figure 1: *Bone Marrow smear showing erythroid hyperplasia*

Examination of Gastrointestinal system reveals almost normal except lips, mouth, oral cavity are markedly pallor. Angular stomatitis is present. There is 2 aphthous ulcers present at oral cavity. One is at the anterior surface of the tongue, measuring about 1×1 cm and another is at the left buccal mucosa, measuring about 4×2 cm. No organomegaly is present. Examination of Cardiovascular system reveals only systolic murmur in the apical area. Examination of Nervous system reveals no abnormality except fundus is pale.

Investigation of the patient reveals Haemoglobin 2.3 g/dl, ESR 110mm, WBC 2.54×10^3/µl, RBC 0.74×10v / µl, Platelet 224×10^3/µl, Neutrophil 22.9%, Lymphocyte 72.8%, HCT 7.1%. Reticulocyte 7.1%, PBF - Normocytic anaemia with leucopenia with few atypical cells. S. LDH - 1331U/L , S. Bilirubin (Total) - 2.81mg/dl , S. Bilirubin (Total) – 1.0 mg/dl, Direct – 0.2 mg/dl, Indirect – 0.8 mg/dl, Coomb's test (Direct &Indirect) – Negative , ANA – Negative. USG of W/A – Mild Hepatomegaly, Bilateral Larger Kidney (? Reactive Changes). S. Vitamin B• , and S. Iron Profile are normal. Urine for haemoglobin was negative. Bone Marrow Study - Hyperactive marrow with dimorphic erythroid and megakaryocytic hyperplasia.

Flow cytometric analysis shows a 63.8% PNH clone within the RBCs and granulocytes. Patient was treated symptomatically with broad spectrum antibiotic, steroid and haematinics and his condition improved and now he is on outpatient follow up. Eculizumab couldn't be used because of its non availability.

Discussion:

PNH is a clonal hemopoietic stem cell disorder that manifest's as hemolytic anaemia, bone marrow failure and thrombosis.[1,2,4] It occurs due to acquired somatic mutation of PIG A (phosphatidyl inositol glycan class A) gene. This encodes an enzyme that generates glycosyl phosphatidyl inositol, a membrane anchor. The complement regulatory protein CD55 (Decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis) are attached to haematopoetic cells by these GPI- anchor protein. As a consequence of mutation, in PNH, cells are more susceptible to complement mediated intravascular haemolysis that is the primary clinical manifestation of this disease.[5] In addition to complement mediated intravascular haemolysis, an element of bone marrow failure is present in all patients. The term PNH is usually imprecise on macroscopic haemoglobinuria. But that is found in only one quarter of affected individual at presentation. In these patient however disease is characterized by symptoms of lethargy, malaise, asthenia, thrombocytopenia, leucopenia, aplastic anaemia, thrombosis involving unusual sites and by laboratory evidence of chronic, low grade intravascular haemolysis[1]. Therefore, a high index of suspicion is needed to diagnose such cases.

Flow cytomtric analysis using antibodies directed against GPI-AP is the most sensitive and confirmatory tool for diagnosis such cases.[6]The FLAER is also commonly being used for diagnosis of PNH.[7] Other supportive laboratory features are Complete blood count which shows moderate

to severe anemia, high reticulocyte count,sometimes bicytopenia or pancytopenia.And also increased levels of unconjugated bilirubin, low concentration of haptoglobin, marked elevation of LDH. Urine examination reveals haemoglobinuria. Bone marrow usually shows erythoid hyperplasia.

Terminal complement inhibition with Eculizumab (a humanized monoclonal antibody) is highly effective.[8] However it is very expensive and lifelong treatment is required. Allogenic bone marrow transplantation is still only curative therapy.[2]

Supportive treatment measures include – (a) Blood transfusion to maintain haemoglobin level, (b) Corticosteroid to reduce haemolysis, (c) Anticoagulant therapy for venous thrombosis. (d) Iron supplementation.

Conclusion:

There is a trend to diagnose PNH based on macroscopic haemoglobinuria. Here we report this case to create awareness among physicians that the diagnosis of PNH must be considered in any patient who has the signs and symptoms of intravascular haemolysis of undefined cause with or without macroscopic haemoglobinuria. So, we can early diagnose the case and lessen patient's sufferings.

Conflict of interest: None.

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