CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3246824

Available online at: http://www.iajps.com *Review Article*

DIAGNOSIS AND TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA WITH COEXISTING APLASTIC ANEMIA IN A 37-YEAR OLD SAUDI MALE: A CASE REPORT WITH REVIEW OF LITERATURE

[1]Fatemah A. Al-Dahneen, [2]Mohammed S. Al-Hassan, [3]Fatemah M. Al-Essa, [4]Ali S. Al-Mutair, [5]Gamal Ghanem Mohamed Mostafa, [6]Sawsan A. Omer.

[1]MBBS ,King Faisal University , Medical Resident in King Fahad Hospital-Hufof ,KSA. [2]MBBS ,Dammam University , Medical Resident in King Fahad Hospital-Hufof ,KSA, [3]MBBS ,King Faisal University , Medical Resident King Fahad Hospital-Hufof ,KSA , [4]MBBS ,Dammam University , Medical Resident in King Fahad Hospital-Hufof ,KSA, , [5]MBBS Faculty of Medicine , Assiut University -Egypt , MD in Internal Medicine ; Assiut University-Egypt, Lecturer of Internal Medicine ;Faculty of Medicine ; Aswan University, Consultant Clinical Haematology; King Fahad Hofuf Hospital, KFHH-HBDC, [6]MBBS ,University of Khartoum, Sudan. MRCPI, Ieland.

Article Received: April 2019 **Accepted:** May 2019 **Published:** June 2019

Abstract:

Introduction: *paroxysmal nocturnal hemoglobinuria (PNH) is a very rare acquired disorder of hematopoietic stem cells and a life threatening disease ; characterized by compliment mediated hemolytic anemia, thrombosis and impaired bone marrow function. There are only over 4000 patients in the international PNH registry. In this report we will describe a case of a Saudi male patient diagnosed with PNH.*

Case report: *A 37 year old male patient presented to our hospital (King Fahad Hospital Hufof) with shortness of breath, palpitation and fatigability; on a background history of multiple prior presentations with red urine. His investigations showed non autoimmune hemolytic anemia and leucopenia . After an extensive work-up, he was found to have paroxysmal nocturnal hemoglobinuria with Aplastic Anemia which requires careful evaluation and management as it is associated with morbidity and mortality if not treated properly. Conclusion: Physicians needs high index of suspicion for the diagnosis of PNH to avoid serious complications of the disease.*

Key words: *paroxysmal nocturnal hemoglobinuria, aplastic anaemia.*

Corresponding author:
Fatemah A. Al-Dahneen,
MBBS, King Faisal University,
Medical Resident in King Fahad Hospital-Hufof ,KSA.

QR code

Please cite this article in press Fatemah A. Al-Dahneen et al., ***Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria with Coexisting Aplastic Anemia in A 37-Year Old Saudi Male: A Case Report with Review of Literature****., Indo Am. J. P. Sci, 2019; 06(06).*

INTRODUCTION:

Paroxysmal nocturnal hemoglobinuria is a rare hematological disorder which was one of the first hematological diseases to be clarified by clinical picture only and has been diagnosed by reliable investigations for more than half of century. (1). It is characterized by triad of hemolysis, thrombosis & peripheral cytopenias (2). The overall prevalence is 1-5 cases per million (3). It is caused by mutation in phosphatidylinositol glycan class A (PIG-A) gene which leads to decrease or absence of glycosylphosphatidylinositol (GPI)-linked proteins (4). Absence of the two (GPI)-anchored proteins, CD55 and CD59, is responsible of uncontrolled complement activation that leads to the clinical manifestations of the disease (2). The approved treatments for PNH are Eculizumab, Ravulizumab (monoclonal antibodies that cause terminal complement inhibition) and allogeneic hematopoietic cell transplantation (HCT) (5, 6).PNH is the most common hematopoietic disorder in patients with acquired aplastic anemia. (7).

Case report OF PNH/AA: PNH With Coexisting Aplastic Anemia:

37 year-old Saudi male previously healthy, initially referred from primary health care as patient had dizziness, shortness of breath, palpitation; hematuria and easily fatigue that started about two months before presentation to urology clinic and aftet full investigations patient was referred from urology department to medical department as a case of unexplained hematuria with leucopenia and anemia.His fatigue was in form of difficulty to carry daily activities and was increasing progressively. He reported to notice his skin turn yellow sometimes. Also, he noticed passage of red urine 2 to 3 times per week that occurred mainly in the morning after wake up, not associated with dysuria or abdominal pain. No obvious bleeding from other orifices .There was no fever or change in bowel habits. No allergy to food (fava bean on recent intake). No history of drug intake. In systemic review of systems he gave history of erectile dysfunction and mild lower back pain. No family history of similar conditions. He is nonsmoker and not consuming alcohol. On admission, vital signs were normal apart from tachycardia with pulse rate of 121/ minute. On examination he was conscious and oriented to time, place and person. He has mildly icteric sclera. The rest of examination was unremarkable. His investigations on admission were notable for : CBC Show Bicytopenia (Leucopenia and and Macrocytic Anemia (WBC 2.41 , Neutrophil 32% , Monocyte 26 % , Hb 8.8 g/dl , MCV 104.5 , PLATLET 225), No Iron deficiency (serum ferritin 72.6 ng/ml), Normal Serum Vitamin B12 and Serum Folate . High liver enzymes (AST 153 U/L, ALT 52 U/L), hyperbilirubinemia (Total bilirubin 22 umol/L, direct bilirubin
3.7 umol/L), High LDH (1795 U/L), Negative direct coombs test, Normal Hb electrophoresis and G6PD enzyme level. Negative ANA .Normal PT,PTT,INR. Celiac profile, HIV, hepatitis B and C serology were all negative. Urinalysis was positive for occult blood with normal urine sediment. Abdominal ultrasound was unremarkable. Peripheral blood smear showed polychromasia , occasional macrocytes, anisocytosis , fragmented RBCs with monocytosis . Bone marrow aspirate and biopsy showed hypocellularity with no abnormal cells or fibrosis. Peripheral blood flow cytometry revealed evidence of absent CD55 & CD59 (PNH clones) with granulocyte of 46.2%, monocyte of 94.2% and RBC of 61.5%.

Patient was stabilized with two units of packed red blood cell in first day of his presentation and was discharged with ciprofloxacin for one week & received meningococcal vaccine. After that he received first dose of Eculizumab. On follow up ; patient has good response for treatment , symptoms improved and no more blood transfusion; last Hb was 12.9 , no evidence of hemolysis but still leucopenic WBC 1.64 but no evidence of recurrent infection and no suitable donor for BM transplant ;patient was put on eculizumab intravenously every 2 weeks with good response.

DISCUSSION:

PNH is an acquired clonal hematopoietic stem cell disorder that can present with non- autoimmune hemolytic anemia and unusual site of thrombosis. Mutation in PIG-A gene causes complete or partial deficiency of CD55 and CD59 causing uncontrolled complement activation leading to hemolytic anemia and other PNH symptoms. Even though the responsible gene is located on X chromosome, it almost exists equally in both males and females since it is an acquired disorder. PNH is characterized by both intravascular hemolysis and extravascular hemolysis. Intravascular hemolysis plays important role in disease pathophysiology. Hemolysis can cause severe anemia, jaundice and dark urine.

Intravascular hemolysis will lead to free hemoglobin in blood which can affect kidneys causing acute or chronic kidney disease. Other complication of free hemoglobin include pulmonary hypertension and smooth muscle spasm such as dysphagia, abdominal pain and erectile dysfunction (8).

Thrombosis is considered one of the most important complications of PNH and is the major cause for

death in these patients (9). It can affect both arteries and veins, but veins are more commonly involved. It can present in unusual site such as portal veins, hepatic veins and cerebral veins. PNH can be complicated by other bone marrow disorders like aplastic anemia, myelodysplastic syndrome and leukemia. Unexplained non-autoimmune hemolytic anemia and unusual site of deep venous thrombosis are considered important clues for the diagnosis. In patients with hemolytic anemia, direct coombs test will be negative as the hemolysis is complement-mediated (not antibody-mediated) and peripheral blood smear will not show significant schistocytes as these are seen in microangiopathic hemolytic anemia.

The diagnostic test for PNH is peripheral blood flow cytometry which can determine whether cells contain glycosylphosphatidylinositol (GPI)-anchored proteins (CD55 or CD59) or not.

Diagnosis will require at least 2 lineages or more having deficiency in CD55 or CD59 (10). In this case report; our patient had hemolysis which was not explained by routine investigations. He also had bicytopenia & intermittent hematuria with negative red blood cells in his urine which raised our suspicion toward PNH. He also had erectile dysfunction. Eculizumab is the first drug to be approved for treating PNH. Based on 2 randomized controlled trials, it showed improvement in Hb level and decreased blood transfusion requirement, in addition ; it reduces the risk for thrombosis. Eculizumab has been successfully shown to prevent complications of PNH and was proven to improve quality of life in patients with PNH. (11).Ravulizumab which was recently approved by American FDA
(12) has the advantage of longer half-life compared to Eculizumab (Ravulizumab is given every 8 weeks compared to Ravulizumab which is given every 2 weeks). Hematopoietic stem cell transplantation should be considered for patients with resistance to monoclonal antibody therapy or patients with concomitant aplastic anemia or leukemia.

CONCLUSION:

Since PNH can cause significant complications such as deep venous thrombosis, early diagnosis and intervention are very crucial in order to decrease morbidity and mortality associated with the disease. Diagnosis, however, can be difficult due to its rarity and atypical presentation. Thus, physician should have high index of suspicion for PNH whenever he faces a patient with unexplained non-autoimmune hemolytic anemia or unusual site of deep venous thrombosis.

REFERENCES:

1. Rosse WF. Epidemiology of PNH. Lancet. 1996 Aug 31;348(9027):560. PubMed PMID: 8774563. (http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)64792-7/fulltext)
2. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014 Oct 30;124(18):2804-11. doi: 10.1182/blood-2014-02-522128. Epub 2014 Sep 18. Review. PubMed PMID: 25237200; PubMed Central PMCID: PMC4215311. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215311/)
3. Risitano AM, Rotoli B. Paroxysmal nocturnal hemoglobinuria: pathophysiology, natural history and treatment options in the era of biological agents. Biologics. 2008 Jun;2(2):205-22. PubMed PMID: 19707355; PubMed Central PMCID: PMC2721357. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721357/#b85-btt-2-205)
4. Sahin F, Yilmaz AF, Ozkan MC, Gokmen NM, Saydam G. PNH is a debilitating, fatal but treatable disease: same disease, different clinical presentations. Am J Blood Res. 2015 Jun 15;5(1):30-3. eCollection 2015. PubMed PMID: 26171282; PubMed Central PMCID: PMC4497495. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4497495/)
5. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014 Oct 30;124(18):2804-11. doi: 10.1182/blood 2014-02-522128. Epub 2014 Sep 18. Review. PubMed PMID: 25237200; PubMed Central PMCID: PMC4215311. (https://www.ncbi.nlm.nih.gov/pubmed?term=25237200)
6. McKeage K. Ravulizumab: First Global Approval. Drugs. 2019 Feb;79(3):347-352. doi: 10.1007/s40265-019-01068-2. PubMed PMID: 30767127. (https://www.ncbi.nlm.nih.gov/pubmed/30767127)
7. Oved JH, et al. pediatr transplant 2019.PubMed. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. JAMA. 2005 Apr 6;293(13):1653-62. Review. PubMed PMID: 15811985. (https://www.ncbi.nlm.nih.gov/pubmed/15811985)
8. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood.

2013 Jun 20;121(25):4985-96; quiz 5105. doi: 91182/blood-2012-09-311381. Epub 2013 Apr 22. Review. PubMed PMID: 23610373. (https://www.ncbi.nlm.nih.gov/pubmed/8652849)

9. Hall SE, Rosse WF. The use of monoclonal antibodies and flow cytometry in the diagnosis of paroxysmal nocturnal hemoglobinuria. Blood. 1996 Jun 15;87(12):5332-40. PubMed PMID: 8652849. (https://www.ncbi.nlm.nih.gov/pubmed/8652849)
10. Lauritsch-Hernandez LS , et al. Eculizumab application during pregnancy in a patient with paraxosmal nocturnal haemglobinuria: A case report with review of literture. Clin Case Rep.2018 .PubMed.
11. McKeage K. Ravulizumab: First Global Approval. Drugs. 2019 Feb;79(3):347-352. doi: 10.1007/s40265-019-01068-2. PubMed PMID: 30767127. (https://www.ncbi.nlm.nih.gov/pubmed/30767127)