International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 6(D); June 2018; Page No. 13373-13375
DOI: http://dx.doi.org/10.24327/ijcar.2018.13375.2383

Case Report

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PRESENTING AS NON-RESPONDING MEGALOBLASTIC ANEMIA IN AN ADULT; A CASE REPORT

Praphull Deepankar[1*]., Ashok Kumar[2]., Naresh Kumar[3] and Gitanjali[4]

[1,2,3]General Medicine, IGIMS, Patna
[4]Narayan Medical College & Hospital, Sasaram (BIHAR)

A R T I C L E I N F O

Article History:

Received 11th March, 2018
Received in revised form 6th April, 2018 Accepted 26th May, 2018
Published online 28th June, 2018

Key words:

Paroxymal nocturnal hemoglobinuria, PNH, pancytopenia, CD55, CD59

A B S T R A C T

Paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by intravascular hemolysis, bone marrow failure and venous thrombosis, is an acquired clonal disorder associated with a somatic mutation in a totipotent hematopoietic stem cell. It is a rare type of acquired hemolytic anemia that is frequently associated with pancytopenia. One such presentation was seen in a middle aged male who had history of severe anemia and jaundice. He was diagnosed to have pancytopenia, intravascular hemolysis, low vitamin B12 and folic acid level with responding hyperplastic marrow and on further workup was found to be a case of PNH.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH), is a rare hematological disorder, affecting all populations throughout the world with prevalence estimated to be up to 5 per million. It is characterized by the formation of defective erythrocytes, granulocytes, and platelets resulting in abnormal sensitivity of red blood cells to lysis by complement system. It is an acquired clonal hematological disorder, caused by a somatic mutation in the X-linked PIG-A gene which is required for the formation of glycosylphosphatidylinositol (GPI) anchored proteins like CD55, CD59 and many others on erythrocyte surfaces. The lack of GPI-linked proteins leads to the clinical features like chronic intravascular hemolysis and thromboembolism.[1] Clinically this disorder is characterized by chronic hemolytic anemia with acute episodes, thrombosis and bone marrow failure. Because PNH is not common, delay in diagnosis is frequent in patients with PNH, and this has a considerable impact on patient management and prognosis. [2] The present study is a case report of middle aged man, presenting with features of megaloblastic anemia, unresponsive to hematinic treatment and diagnosed PNH later on.

Case Report

A 34 yrs. old male patient presented to the casualty with complaints of breathlessness on exertion, and easy fatigability for last 2 months followed by yellow discoloration of eyes for7 days.

Corresponding author:* **Praphull Deepankar
General Medicine, IGIMS, Patna

He had no history of orthopnea, paroxysmal nocturnal dyspnea, hematuria, melena and oliguria. No history of bleeding manifestations, abdominal pain & swelling were present. No past history of diabetes, hypertension or jaundice was present. On physical examination he had severe pallor, mild icterus and mild bilateral pitting type of pedal edema, without having clubbing, lymphadenopathy, skin rashes, and bony tenderness. Vital parameters were normal. On examination, hepatosplenomegaly was present while respiratory, cardiovascular and central nervous systems were normal.

With these findings he was admitted for further work up. Investigations revealed hemoglobin 5.6 gm./dl, hematocrit 24%, total leucocyte count 2600mm^3/ml (Polymorphs-64%, Lymphocytes- 34%, Monocytes-2%), platelets-62,000/ml, reticulocytes-4.9%, MCV-118 fl, and peripheral smear showing macrocytosis and anisocytosis. Further investigations showed total bilirubin 4.2mg/dl, AST 65 unit/ l, ALT 25 unit/l, alkaline phosphatase 63 unit/l and LDH 1105 unit/l. Serum vitamin- B_{12} – 176 pg/ml (normal range-197-866), serum folic acid– 2.0 (normal- 2.78- 20.0 ng/ml). Kidney function test was normal. The tests for hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus were negative. Chest X-Ray and 2D echo were normal. With these features of pancytopenia and hemolysis, bone marrow aspiration was performed, which revealed erythroid hyperplasia with features of megaloblastic maturation. Ultrasound abdomen showed hepatosplenomegaly.

Course During Hospital Stay

Diagnosis of nutritional megaloblastic anemia was considered and intravenous supplementation of vitamin B12 and folic acid started along with other symptomatic measure. After 5 days of treatment patient was assessed again. His symptoms persisted and his jaundice aggravated further. Patient's routine investigation ordered again. Repeat investigations showed decrease in Hb. Serum bilirubin increased along with serum LDH. (Table.1)

Table 1 Investigation Profile of the Case

	DAY 1	**DAY 7**
Hb	**5.6**	**3.9**
TLC	2600	3200
PLATELET COUNT	62000	90000
RETIC. COUNT	4.9%	8%
MCV	118	106
T.BILIRUBIN	4.2	8.2
(Direct/Indirect)	(0.8/3.8)	(1.1/7.1)
SGOT/SGPT	65/25	58/48
S. LDH	1200	6440

In view of severe continued hemolytic anemia with responding hyperplastic bone marrow, investigations were ordered to find the underlying causes of hemolysis. The hemoglobin electrophoresis and G6PD level were normal. The direct and indirect coomb's test, antinuclear antibody and VDRL were all negative. Peripheral blood Flowcytometry for PNH CD markers was sent. Immunphenotyping study showed 82.3% granulocytes negative for CD55, 87.4% granulocytes negative for CD59, 81.5% granulocytes were double negative for CD55 and CD59 (PNH clone). These findings confirmed the diagnosis of paroxysmal nocturnal hemoglobinuria. Patient was managed symptomatically with blood transfusion and referred to Hematology Centre for further management/bone marrow transplant.

DISCUSSION

Paroxysmal nocturnal hemoglobinuria arises as a result of nonmalignant clonal expansion of one or several Hematopoietic stem cells (HSCs) that have acquired a somatic mutation of PIGA gene on X chromosome which encodes an essential enzyme for the synthesis of GPI Moiety. GPI moiety serves as a membrane anchor for more than 20 proteins of diverse function that are normally expressed on hematopoietic cells. The lack of these GPI-linked proteins due to mutation leads to the primary clinical features like chronic intravascular hemolytic anemia due to complement mediated intravascular hemolysis and thromboembolism due to thrombophilia. [1]

The illness ranges from a mild, clinically benign process to a chronically debilitating, potentially fatal disease. The diagnosis is made most frequently in the fourth to fifth decades of life, but it may be encountered in childhood and in old age. Both genders are affected, with a slight female predominance. The disease has no familial predominance. The most common presentation of PNH is fatigue (80%), followed by dyspnea (64%) and hemoglobinuria (62%). Thrombosis is reported in only 16% of cases, but it represents the most common cause of mortality in PNH. The venous system – especially portal, mesenteric, and hepatic veins – is more commonly affected than is the arterial system.And intracerebral sites are less commonly involved than intra-abdominal sites. The major risk factors for thrombosis are the proportion of PNH granulocytes (PNH clone size) and the degree of intravascular hemolysis. Europeans have also been shown to be at increased risk for thrombosis when compared to Asian patients. [3]

In PNH, the most common finding is normocytic to macrocytic anemia. If there is an iron loss due to chronic hemoglobinuria, then microcytic anemia may be presentation of the disease.Usually, bone marrow is responsive showing erythroid hyperplasia. Nakamura *et al*. have presented a 29-year-old female with PNH case presenting with profound pancytopenia, like in our case. [4]

Our patient presented with progressive anemia unresponsive to hematinic, persistent pancytopenia and jaundice, characteristic features of PNH. He did not give history of passage of cola-colored urine. Although hemolysis occurs throughout the day but patients may complain for passing red concentrated urine in the morning. As urine is more concentrated in the morning, this is when color is more pronounced. The hypothesis of increased hemolysis at night during sleep due to acidosis or low steroid levels is not supported by studies. Our patient had no thrombotic episodes at the time of diagnosis.

The clinical course of PNH is quite variable. It usually runs a chronic course with above mentioned symptoms, and may evolve into aplastic anemia, myelodysplastic syndrome or even acute leukemia. Very rarely the abnormal clone may completely disappear and the patient be cured of the disease spontaneously.[5]

The gold standard test to diagnose PNH is Flowcytometry, which can be carried out on granulocytes as well as on red blood cells. Diagnosis of PNH is confirmed with peripheral blood Flowcytometry by detecting the absence of GPI-APs on $\geq$ 2 lineages (Should be at least 5% in RBCs & 20% in PMNs) with a reagent known as fluorescent aerolysin (FLAER). [6]

The treatment available for hemolytic anemia in PNH include blood transfusions, pulse prednisolone for acute attacks, folic acid, iron supplements, low dose prednisolone and eculizumab (humanized monoclonal antibody against complement C5) for chronic hemolysis. Intravascular hemolysis is the dominant feature of classic PNH, and this process is blocked by the complement inhibitor eculizumab with decreased need of blood transfusions and marked improvement in signs and symptoms and quality of life.[7]

The thrombotic tendency of PNH also appears to be ameliorated by eculizumab. The 5 year survival of patients with PNH prior to eculizumab therapy was 67% and has improved to 96% in patients who used the monoclonal antibody. The medication also decreased the risk for thrombotic events from 6% per year to less than 1% per year. It has been shown that eculizumab therapy, which is effective in decreasing hemolysis, can also decrease the risk for venous thrombosis. The drug has no effect on the bone marrow failure component of the disease. [8] Two multinational phase 3 trials, the TRIUMPH and SHEPHERD trials, concluded that eculizumab is highly effective in stopping intravascular hemolysis, decreasing the need for red cell transfusions with >70% achieving transfusion independence, improving quality of life, and reducing the risk of thrombosis. [9] An ongoing controversy in PNH is management of thrombosis. No consensus exists for primary prophylaxis, given the unpredictability of thromboembolic events. Primary prophylaxis should be used for patients with PNH clones larger than 50% or those with additional genetic risk for

thrombosis, including ethnicity. As for secondary prophylaxis, patients having any thromboembolic event should remain on lifelong anticoagulation. Both low molecular weight heparin (LMWH) and warfarin at different therapeutic ranges are utilized. [10]

Severe anemia, thrombosis, renal insufficiency, and dyspnea are all strong indications to initiate therapy. Corticosteroids may improve hemoglobin levels and reduce hemolysis, but their minimal benefit is overshadowed by their long-term toxicity. Allogeneic stem cell transplant is an option for patients with severe aplastic anemia or those who are unresponsive to eculizumab therapy. [11]

CONCLUSION

In this case report, we presented a case of PNH patient, who was initially diagnosed with megaloblastic anemia due to the presence of pancytopenia, low vitamin B12 level with responsive hyperplastic bone marrow. However, during hospital stay, because of severe anemia with continued hemolysis and reticulocytosis, PNH was suspected. Clinician should always consider PNH as differential diagnosis of pancytopenia in an adult patient when intravascular hemolysis is prominent features.

References

1. Shichishima T and Noji H. A new aspect of the molecular pathogenesis of paroxysmal nocturnal hemoglobinuria Hematology. 2002 Aug; 7(4): 211-27.
2. Luzzatto L: Hemolytic anemia and anemia due to acute blood loss. Harrison's Principles of Internal Medicine. 18th edition. Edited by Lango DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. New York: McGraw-Hill; 2011:872–897.
3. Rositano AM, Rotoli B. Paroxysmal nocturnal hemoglobinuria: pathophysiology, natural history and treatment options in the era of biological agents. Biologics: Targets & Therapy. 2008;2(2):205-222.
4. Abdul RaufMemon, Rizwan Khan, Mohammad Uzair Abdul Rauf and KashifShafique. Paroxysmal nocturnal hemoglobinuria presenting as cerebral venous sinus thrombosis: a case report. *International Archives of Medicine.* 2014; 7:39.
5. Hillmen P, Lewis SM, Bessler M, *et al*. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med.* 1995; 333:1253-1258.
6. Meyers G, Parker CJ. Management issues in paroxysmal nocturnal hemoglobinuria. *Int J Hematol*. 2003 Feb; 77(2): 125-32.
7. Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, Cullen MJ, Richards SJ, Rollins SA, Mojcik CF, Rother RP: Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2004, 350:552-559.
8. Parker C: Eculizumab for paroxysmal nocturnal hemoglobinuria. *Lancet* 2009, 373(9665):759–767.
9. Brodsky RA, Young NS, Antonioli E, *et al*. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood.* 2008; 111: 1840-1847.
10. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*.2014; 124(18):2804-2811.
11. Mohammed, A.A., EL-Tanni, H., Atiah, T.AM. *et al*. Paroxysmal Nocturnal Hemoglobinuria: From Bench to Bed. *Indian Journal of Hematology and Blood Transfusion* (2016) 32: 383.

How to cite this article:

Praphull Deepankar *et al* (2018) 'Paroxysmal Nocturnal Hemoglobinuria Presenting as Non-Responding Megaloblastic Anemia in An Adult; A Case Report', *International Journal of Current Advanced Research,* 07(6), pp. 13373-13375.
DOI: http://dx.doi.org/10.24327/ijcar.2018.13375.2383

****