ISSN: 2395-6429

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

IJCMPR

Available Online at http://www.journalcmpr.com

DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20170036

CASE REPORT

A RARE PRESENTATION OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) – A CASE REPORT

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ARTICLE INFO

Article History:

Received 16th January, 2017
Received in revised form 28th February, 2017
Accepted 15th March, 2017
Published online 28th April, 2017

Key words:

PNH (Paroxysmal nocturnal hemoglobinuria) , Glycosyl Phosphatidylinositol (GPI), PND(paroxysmal nocturnal dyspnea),PMNL(polymorphonuclear leukocytes) , HSC(Hematopoietic Stem Cells), NO(nitric oxide) , PIGA (Phosphatidylinositol Glycan-Class A), FCM - Flow Cytometry

ABSTRACT

A 34 Yr old female presented with pancytopenia and inferior venacaval thrombosis. Bone marrow examination revealed aplastic anemia. Diagnosis of PNH was made in this patient by flow cytometry Classically PNH presents with episodic hemolysis resulting in hemoglobinuria but this patient presented with above features which is an unusual presentation.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal hematopoietic stem cell disorder which results in complement mediated RBC membrane lysis. The underlying cause is somatic mutation of the X-linked phosphatidyl-inositol-glycan gene [PIGA] which results in a partial or absolute deficiency of GPI-linked proteins in the progeny of affected stem cells. The lack of GPI-linked proteins leads to the clinical features like chronic intravascular hemolysis (due to cd55 & cd59 deficiency) and thromboembolism due to thrombophilia. Thrombophilia is a major cause of morbidity and mortality in PNH .The role of GPI-AP in bone marrow failure which is often associated with PNH is less clear.

We report a case of aplastic anemia with inferior venacaval thrombosis due to PNH in a middle aged female diagnosed by performing flowcytometry for PNH CD markers on peripheral blood granulocytes and red blood cells following International Clinical Cytometry Society (ICCS) guidelines.

Case Report

A 34 Yr old female patient presented to the hospital with complaints of breathlessness on exertion, easy fatiguability and mild bilateral pedal edema of 2 months duration. She had no history of orthopnea, PND & oliguria. No history of blood transfusions, drug intake, bleeding manifestations, abdominal pain & swelling. No history of jaundice in the past. Patient had oligomenorrhoea since 3 months. No history of consanguinity. On physical Examination she had severe pallor and mild bilateral pitting type of pedal edema with no icterus, no clubbing and no lymphadenopathy. Vital parameters were normal. On examination respiratory, cardiovascular & central nervous system were normal.

Laboratory Investigations revealed -CBP –Hemoglobin of 3.5 gm/dl with normo to macrocytic RBCs & polychromasia, -with leucopenia (TLC -1500/ mm3) and thrombocytopenia (Platelet Count – 60,000/µl) – S/O-**PANCYTOPENIA** . Reticulocyte count was 1.8%. Serum vitamin- B 12 - 397pg/ml (197-866) & Serum Iron -157 (30-170 µg/dl), Iron Binding Capacity -322 µg/dl (250-450) , Percent Transferrin Saturation – 43 %(13-45) and Serum Ferritin – 48 (15 – 300 Ug/L)were normal . Bone Marrow Biopsy (done before the packed cell transfusions) S/O - **HYPOCELLULAR MARROW WITH <30% CELLULARITY**. Her liver function tests showed total

proteins of - 6.1 gm/dl with albumin-2.1gm/dl, globulin-3.7gm/dl & total bilirubin-1.5mg/dl , conjugated bilirubin - 0.3mg/dl, ALT-27IU/L, AST–35IU/L, Alkaline phosphatase – 110 U/L. Sr-creatinine (0.6mg/dl) , blood urea (14 mg/dl) , Random blood sugars-83mg/dl and complete urine examination were normal. Urine hemosiderin – negative. Serum LDH levels were normal (190 U/L). Viral markers (HIV, HbSag, Anti-Hcv) were non reactive. Chest X-Ray was normal. 2D-echo-normal. ULTRASOUND - WHOLE ABDOMEN -S/O Normal liver & spleen with multiple dilated tortuous vessels noted at the splenic hilum with normal portal vein.

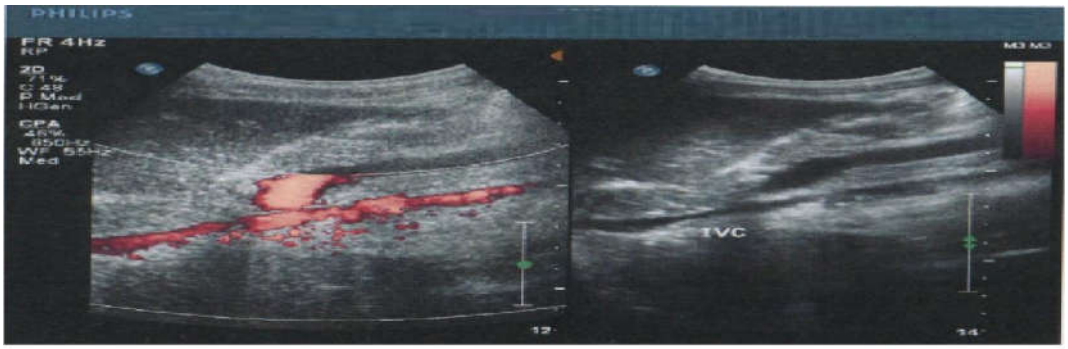
Doppler evaluation of spleno-portal venous system revealed normal liver, portal Vein(normal diameter (9mm) & spleen with multiple dilated tortuous vessels noted at the splenic hilum with irregular echogenic partial thrombus noted in intrahepatic inferior venacava for ~ 3-4 cm length causing upto 50% luminal narrowing , hepatic veins were patent with loss of phasic variation UPPER G I ENDOSCOPY – normal study. Bleeding time, clotting time, prothrombin time (14.5/ Sec MNPT-13.8 & INR -1.27) & APTT (32.2 Sec) were normal. ANA levels, coombs test (both direct and indirect) were negative. Screening for lupus anticoagulant –was negative, Protein C & S- were normal, Serum homocysteine - 6.12 (5-12micromol/L) (N).

on monocytes suggestive of PNH clone in granulocytic series. A final diagnosis of PAROXYSMAL NOCTURNAL HEMOGLOBINURIA with IVC THROMBOSIS & APLASTIC ANEMIA was made.

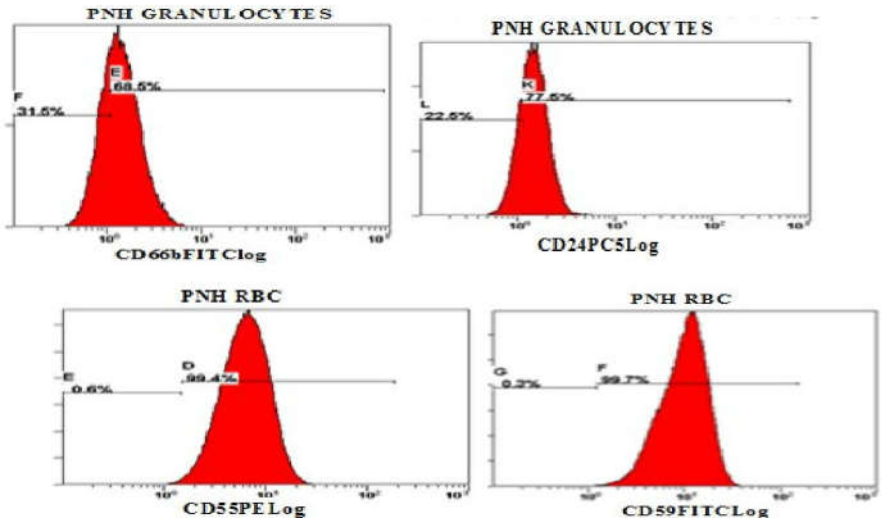
Patient was treated with 3 units of packed cell transfusions. Inj Enoxaparin & Tab Warfarin were given for the IVC thrombus & PT – INR was maintained between 2-3. Oral cyclosporine was started and was kept on regular follow up. Triple phase CT Abdomen done 2 months later revealed complete resolution of the IVC thrombus with improved complete blood picture & symptoms.

DISCUSSION

Paroxysmal nocturnal hemoglobinuria arises as a result of nonmalignant clonal expansion of one or several 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. As a consequence of the mutation, progeny of affected stem cells (erythrocytes, granulocytes, monocytes, lymphocytes & platelets) are deficient in all Gpi-Anchored proteins (Gpi-Aps). The lack of these GPI-linked proteins leads to the primary clinical features like chronic intravascular hemolytic anaemia due to



Power Doppler & grey scale images shows decreased caliber of IVC with partial echogenic thrombus



Peripheral blood Flowcytometry for PNH CDmarkers was done. Results of Flowcytometry-0.6 % & 0.3% of clones of CD-55 & CD-59 respectively on RBCs, 22.5 % & 31.5% of CD -24 & CD-66b on granulocytes with 2% of CD 55 markers

complement mediated intravascular hemolysis and thromboembolism due to thrombophilia. PNH frequently arises in association with a defined bone marrow failure process, particularly aplastic anemia and, to a lesser extent, low-grade myelodysplastic syndrome (MDS). A close association exists between PNH & certain bone marrow failure syndromes, but the basis of this association is incompletely understood [1].PNH usually begins insidiously with clinically apparent hemoglobinuria. The illness ranges from a mild, clinically benign process to a chronically debilitating, potentially lethal disease. The diagnosis is made most frequently in the fourth to fifth decades of life, but it is also encountered in childhood and in old age. Both genders are affected, with perhaps a slight female predominance [1]. Its prevalence is estimated to be approximately 5 per million[2]. The disease has no familial tendency.

Clinically PNH is classified into 3 categories 1) Classic PNH 2) PNH in the setting of another specified bone marrow disorder 3) Subclinical PNH (PNH -Sc) (International Pnh Interest Group). Classic PNH has clinical evidence of intravascular hemolysis with no evidence of defined bone marrow abnormality but have a large Gpi-Ap deficient PMNL PNH Clone (>50%) . PNH in the setting of another specified bone marrow disorder has mild rate of intravascular hemolysis (often with minimal abnormalities of biochemical markers of hemolysis) with a defined underlying marrow abnormality. This category usually has relatively small PMNL (25-50 %) PNH Clones. Patients With PNH -Sc have no clinical or laboratory evidence of hemolysis and approximately 80% of these cases have <1.0% of GPI-Ap–deficient cells.[3]

The primary clinical manifestations of PNH are hemolysis, thrombosis, and marrow failure. Constitutional symptoms (fatigue, lethargy, malaise) dominate the history. Patients frequently experience dysphagia, odynophagia, & male impotence which worsen during hemolytic exacerbations (due to NO deficiency that is a consequence of the sump effect of plasma free hemoglobin). Abdominal pain, acute and chronic renal insufficiency are the other features.

Hemolysis and nocturnal hemoglobinuria is a presenting symptom in approximately 25 percent of patients (occurs due to retention of CO_2 causing a slight fall in blood pH sufficient to activate the alternative pathway of complement system). Thrombophilia is a major cause of morbidity and mortality (about 50%) in PNH. Venous thrombosis, often occurring at unusual sites [hepatic veins and inferior vena cava (Budd-Chiari Syndrome), mesenteric, dermal or cerebral veins], may complicate PNH.

Arterial thrombosis is less common. Thrombosis may be due to Deficiency or absence of other GPI-linked (or associated) proteins: u-PAR, heparan sulfate, TFPI, and proteinase-3 and free hemoglobin released from hemolysis with resultant NO Depletion and Endothelial Dysfunction[4]

The GOLD STANDARD TEST to diagnose PNH is FLOW CYTOMETRY, which can be carried out on granulocytes as well as on red blood cells. PNH clone size can be more accurately enumerated in WBC, because WBC half-life is normal in PNH, whereas RBC half-life, especially for type III (COMPLETE GPI-AP DEFICIENCY), is shortened (APPROX 6 DAYS) due to hemolysis. Furthermore, PNH RBCs, as opposed to WBCs, are diluted by transfusion which additionally diminishes the value of RBCs for evaluation of clonal size. Patients with a PMN clone size of 20% to 25% usually have 3% to 5% PNH erythrocytes (the population of PNH III cells is smaller than the clone size because the complement-sensitive red cells are selectively destroyed intravascularly).

Diagnosis of pnh was made with flowcytometry RESULTS. Clinically this patient had 2nd category of PNH. This particular case highlights unusual presentation of PNH that is inferior venacaval thrombosis in contrast to the usual presentation of hemolysis.

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