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Paroxysmal Nocturnal Haemoglobinuria In Pregnancy: A Case Report

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Abstract
Introduction: Paroxysmal nocturnal haemoglobinuria is a rare clonal disorder of hematopoietic stem cells. It is the only hemolytic anemia with acquired mutation in hematopoietic stem cell where one or several hematopoietic stem cells acquire a somatic mutation of PIGA gene (phosphatidyl inositol glycan class A) which is responsible for production of GPI (Glycosylphosphatidylinositol) anchored proteins resulting in defect in CD55 and CD59 causing intravascular complement mediated hemolysis. Pregnancy worsens the clinical manifestations of Paroxysmal nocturnal haemoglobinuria, increasing maternal and fetal morbidity and mortality.
Case report: A 21 years old primigravida presented with dyspnea and weakness at 30 weeks of pregnancy. Routine investigations revealed severe anemia and thrombocytopenia. Patient required repeated transfusion of red blood cells and platelets. On further probing into past and vigorous investigations, patient was diagnosed with PNH. She did not have any thromboembolic event and delivered at term by a lower segment cesarean section.
Conclusion: Pregnant patients with Paroxysmal nocturnal haemoglobinuria should be watched clinically and by laboratory parameters for any symptoms/signs of hemolysis or thrombosis, and to determine whether to use prophylactic anticoagulants for thrombosis prevention.
Key Word: *Paroxysmal Nocturnal Haemoglobinuria, Pregnancy, PIGA gene*

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I. Introduction

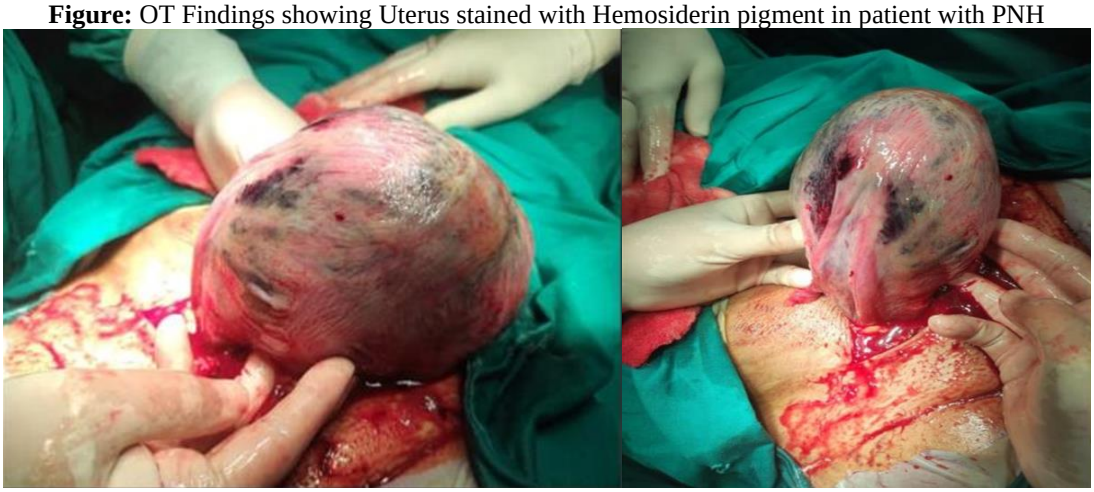
Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired haemolytic anaemia caused by a defect in glycophosphatidylinositol (GPI)-anchored proteins in the cell membrane of bone marrow stem cells, which increases red cell sensitivity to complement, resulting in intravascular haemolysis and haemoglobinuria..(1) PNH typically manifests as haemolytic anaemia, thrombosis, and smooth muscle dystonia, with bone marrow failure in certain cases. It has a worldwide incidence of 1–1.5 cases per million individuals. Pregnancy increases the risk of maternal thrombosis and activates the complement system. Maternal and foetal morbidity and mortality were found to be higher in pregnant PNH patients, prompting the recommendation to avoid pregnancy.(2) The detection and quantification of GPI-deficient populations is critical for selecting the best therapy. Therefore, flow cytometry of GPI-anchored proteins on peripheral blood cells is the gold standard for diagnosis in PNH.(3) Until 2007, the primary treatment for this disorder was supportive, with red blood cell and platelet transfusions, folic acid and iron replenishment, glucocorticoids, and anticoagulant therapy. Bone marrow transplantation looks to be the only potentially curative therapy; however, it carries a 10-20% risk of early mortality. Eculizumab, a humanised monoclonal antibody, has significantly transformed the treatment of PNH. The use of this antibody to treat PNH was approved by the US Food and Drug Administration in March 2007, followed by the European Medicines Agency in June 2007.(4)

II. Case Report

A 21years old primigravida presented to our hospital for routine antenatal visit where routine antenatal investigations revealed moderate anemia in first trimester and was evaluated for the same, iron studies showed iron deficiency anemia hence received oral iron. At 30 weeks, patient presented with complaints of dyspnoea and weakness. Routine investigations revealed haemoglobin of 2.9gm/dl and platelet count of 20,000. On receiving transfusion of packed red blood cell(pRBC) and platelets, patient was discharged from hospital. During routine follow up, when haemoglobin and platelet counts failed to improve, patient was again transfused packed red blood cell and platelets, however there was no improvement in haemoglobin level and platelet counts. On further probing into past and vigorous investigations and evaluation, patient was diagnosed

with PNH on flow cytometry. Patient received anticoagulants and regular transfusions. She did not have any thromboembolic event. Patient was monitored thoroughly and at 37 weeks patient delivered by lower segment caesarean section. Post operative period was uneventful.

Figure: OT Findings showing Uterus stained with Hemosiderin pigment in patient with PNH



III. Discussion

Historically, pregnancy for women with PNH has been associated with significant rates of maternal and foetal mortality. Pregnant women with PNH had a death rate of 8% to 21%, while the foetal death rate was 4% to 9%.(5) The interplay of many factors working on primary, secondary, and tertiary haemostasis makes it difficult to assess the genuine thrombotic risk in such an intricate scenario. With proper care of each component, the pregnancy went successfully without any thrombotic problems or breakthrough haemolysis, and the outcome was favourable for both mother and child. Before the emergence of C5 inhibitors, transfusions were the sole treatment for anaemia in patient with PNH. Unaddressed, the prothrombotic effect of haemolysis was linked to a significant incidence of venous thromboembolism during pregnancy and lower life expectancy, prompting these patients to avoid conception.(6) Early diagnosis of PNH is crucial for treatment and prognosis, however due to varying clinical signs, diagnosis is often delayed.

Flow cytometry is the gold standard for diagnosing and monitoring the patient with PNH. Using the most recent International Clinical Cytometry Society/European Society for Clinical Cell Analysis recommendations, it is possible to detect not only a clone of GPI-defective cells in each of the three types of PNH, but also to identify even a few cells with the PNH phenotype. This test is highly sensitive. Eculizumab, the first monoclonal antibody to inactivate the C5 complement component, was approved for the treatment of PNH in 2007. In 2018, ravulizumab was approved. Both inhibitors impede terminal MAC formation, which prevents blood cell lysis. C5 inhibitors altered the natural progression of the disease. The use of eculizumab considerably lowers the incidence of thrombotic events.(7)

Patient was explained about her condition and was explained about the treatment modality and pros and cons of eculizumab, however patient refused to receive eculizumab therapy due to high cost. Hence patient received anticoagulation with low molecular weight heparin daily and regular transfusion of red blood cells and platelets. No thromboembolic complications were observed and patient underwent caesarean section at term without any complications.

IV. Conclusion

Paroxysmal nocturnal haemoglobinuria in pregnancy is rare but challenging case to diagnose. Pregnant patients with Paroxysmal nocturnal haemoglobinuria should be watched and monitored clinically and by laboratory parameters for any symptoms/signs of hemolysis or thrombosis. Based on our experience from the reported case, Pregnancy is not indicated for people with PNH due to high risk of complications. Experts from both hematology and obstetrics should be involved in patient treatment.

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