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Research Article

Perforation of Ileum Due to Thrombosis in the Course of Paroxysmal Nocturnal Hemoglobinuria: A Case Report

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease which is characterized by hemolysis, thromboses in unexpected sites and multi-organ involvement. Arterial thromboses could result in necrosis and dysfunction of involved organs. In some cases, organ dysfunctions could be fatal as in involvement of heart, small intestine and lung. Eculizumab is a monoclonal antibody which decreases risk of thrombosis and hemolysis in patients with PNH by inhibiting complement system. Hereby, we present a case with acute abdomen which was operated and small intestinal necrosis was detected due to thrombosis which was resulted in PNH undiagnosed until the time of operation. Unexpected thromboses should be carefully investigated in

terms of potential coexistence of PNH associated with multi-organ involvement and treated appropriately.

Keywords: Paroxysmal nocturnal hemoglobinuria (PNH), thrombosis, eculizumab.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder characterized by a defect in the glycosylphosphatidyl-inositol (GPI) anchor protein which results in partial or complete absence of certain GPI-linked proteins. This defect is caused by a mutation in phosphatidylinositol glycan class A *(PIG-A)* gene. Especially the absence of CD55 (DAF: decay accelerating factor) and CD 59 (MIRL; membrane inhibitory of reactive lysis) proteins which are linked to the membrane by GPI anchor proteins leads to increased sensitivity of red blood cells to complement system and results in intravascular hemolysis, generation of inflammatory mediators (Takeda, Miyata et al. 1993), Rosse (1997). PNH is characterized by hemolysis, bone marrow failure with cytopenias and life threatening thrombotic

episodes. Myelodisplastic syndrome and acute leukemia can also be seen in the course of the disease (de Latour, Mary et al. 2008). However, one of the most common causes of mortality and morbidity in PNH patients is thromboembolism. It causes approximately 40-67% deaths with known etiology. The thrombosis preceding diagnosis of PNH is also not uncommon. (de Latour, Mary et al. 2008, Hill, Kelly et al. 2013) The thromboembolism can occur at any site of the body effecting both arteries and veins (Hill, Kelly et al. 2013) Treatment only with anti-coagulant therapy is not sufficient and thrombosis may occur even if patient is actively treated with anti-coagulant therapy. Eculizumab should be added to the treatment of patients with acute thrombosis. Eculizumab is a monoclonal antibody to complement component component C5 which decreases risk of

thrombosis and hemolysis in patients with PNH by inhibiting complement system (Hill, Kelly et al. 2013).

We report a patient presented with mesenteric ischemia and perforation of the ileum and diagnosed as PNH after the partial resection of the ileum.

Clinical Presentation

Eighteen-year-old female patient was admitted to the Emergency Unit (EU) for abdominal pain and palpitation, which were lasting for 10 days. Vital signs were recorded as body temperature 38,8^{o}C, pulse rate 155 beats/min, blood pressure 177/80 mmHg and respiratory rate (22/min). Ascites and hepatosplenomegaly were detected on her physical examination. ECG findings were

indicative of sinus tachycardia. Results of complete blood count analysis were as follows: white blood cell (WBC) = 4950/µl, hemoglobin (Hb) = 8.9 g/ dl, hematocrit (Htc) = 27.2% and platelet count (Plt) = 95000/µl. Blood chemistry results were normal except high lactate dehydrogenase level (LDH: 927 U/ L). Iron parameters, vitamin b12 and folic acid levels were normal.

Abdominal ultrasonography depicted hepatosplenomegaly and portal vein thrombosis, perisplenic, perihepatic and intra-abdominal free fluid collection around pelvic bowel loop, pouch of Douglas and Morrison pouch.

At her medical history, use of oral contraception and spontaneous miscarriage 2 months ago at gestational age of 19 weeks were remarkable.

Patient was hospitalized and enoxaparin (2x 4000IU/0.4ml) was initiated due to portal vein thrombosis. Thorax CT was scanned to rule out the possibility of pulmonary thromboembolism (PTE), resulting with no significant finding.

At 48 hours of admission, patient was assessed due to severe abdominal pain. Physical examination revealed jaundice and sclerotic skin, increase in heart and respiratory rate and abdominal tenderness. She was anemic. The peripheral blood smear revealed hemolysis with spherocytes, polychromasia. Direct and indirect Coombs tests were negative. Serum haptoglobulin level was < 20mg/dl and reticulocyte was 5.4 percent. Biochemistry tests were normal except high LDL level.

In the abdominal CT, thrombosis in portal and splenic vein, mesenteric ischemia were documented. Partial small bowel resection and ileostomy were performed due to necrosis and perforation in terminal ileum. Pathology results included ischemia, necrosis and perforation of terminal ileum.

Patient was monitored at Intensive Care Unit (ICU), resulting with slight improvement. Genetic thrombophilia tests, including Factor V Leiden, Prothrombin G20210 A and methylene-tetrahydrofolate reductase (MTHFR) A1298 mutations, were negative, while only heterozygous MTHR C677T mutation was determined. Protein C, S and antithrombin III levels were in the normal limits. ANA, anti DNA and anticardiolipin antibodies (anticardiolipin – Ig- G: 4 MPL, anti B2 glycoprotein Ig M: 5 GPL U/ML) were negative.

Since she had multiple thromboses without known etiologies at unusual sites and hemolytic anemia, PNH was suspected. The diagnosis was made by flowcytometric method. FLAER/CD24 was used at granulocytes and gated by CD 15. CD 54 was used in erythrocytes and gated by CD 235a. The clone size at granulocytes was 63% and total clone size (type 2 and 3) was 10% at erythrocytes. (Sutherland, Keeney et al. 2012)

She was vaccinated against H. influenza, pneumococcus, N. Meningitis. IV meropenem and eculizumab treatments were initiated simultaneously since the culture of ascite was positive for extended spectrum beta lactamase positive E. *coli.*

After the eculizumab treatment was initiated, hemolysis and pancytopenia can be taken under control. Patient discharged at the second week of the admission.

She is still followed up by Hematology Department with eculizumab treatment in remission with normal hemoglobulin and leucocyte counts and slightly low platelet counts (WBC: 8600/$mm^{3,}$ hb: 12 gr/dl, platlet: 75000/ mm^3) without any need for transfusion or evidence of new thrombosis. The last clone size was 82.21 % at granulocytes.

Discussion

PNH is a rare acquired clonal disease characterized by hemolytic anemia and thrombosis (Hillmen, Lewis et al. 1995). The

erythrocytes become susceptible to complement system due to lack of CD 55 and CD 59 membrane proteins which are anchored to the membrane by GPI proteins. The situation is due to somatic mutation in (PIG-a) gene (Luzzatto 2006). Thrombosis is one of the leading causes of mortality and morbidity in these patients. The thrombosis may occur at any site but mostly abdominal veins are affected. The reason why the intra-abdominal veins are mostly affected is unknown (Hill, Kelly et al. 2013). Thrombosis of visceral organs including liver, mesentery, and spleen may precede the diagnosis of PNH (Hill, Kelly et al. 2013) as in our case. In the medical history of the patient, early miscarriage was remarkable which also could be due to thrombosis in the placenta before the mesentery ischemia. Also oral contraception may contribute the risk of thrombosis in this patient. In this case the diagnosis is confirmed after a serious thrombosis of portal,

spleen and mesenteric veins that leads to resection of the necrotic small intestine.

The mechanism of thrombosis in PNH patients is not well understood. Activation of platelets, complement mediated hemolysis, depleted nitric oxide level, impairment of fibrinolytic system, and inflammatory mediators are possible mechanism (Hill, Kelly et al. 2013). Experimental studies demonstrated that hemoglobin is released during hemolysis, resulting with decrease in release of nitric oxide, and this process increases platelet activation and promotes tendency to thrombosis (Rother, Bell et al. 2005).

Diagnosis is based on demonstrating CD55 and CD59 deficiencies with flow cytometric method. Erythrocyte screening alone will

lead to false negative results if patient has history of recent transfusion or active hemolytic episode. Therefore, granulocytes and monocytes are indicators in determining PNH clone (Savage and Brodsky 2007). In our case, CD55 and CD59 levels were low at level of both granulocytes and erythrocyte membrane

Eculizumab is a monoclonal antibody that binds to the C5 component of complement system and inhibits the complement activation and inhibits terminal complement activation (Parker 2009).. It reduces hemolysis, increases hemoglobulin levels and quality of life and decreases the incidence of thrombosis and improves survival with acceptable adverse effects(Hill, Kelly et al. 2013) (Kelly, Hill et al. 2011) Under the light of all these studies eculizumab becomes important part of the management of PNH patients. Treatment with eculizumab was initiated in our patient

after the diagnosis was confirmed simultaneously with anticoagulation therapy. After the initiation of eculizumab, the hemoglobulin levels increased with decrease in hemolysis and no new thrombotic event developed during the follow up period. She is still in hematologic remission with normal hemoglobulin levels and no signs of hemolysis.

Conclusion

Since PNH can cause severe morbidity and mortality in young patients, we should consider this entity in differential diagnosis of thrombosis especially in young patients who have thrombosis in unusual sites associated with coombs negative hemolytic anemia or cytopenias(Hill, Kelly et al. 2013). We should not

forget that it is a rare entity with diverse clinical presentation with a specific and effective treatment.

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