Successful Management of Obstructive Jaundice due to Gallstones with Eculizumab in a Patient with Paroxysmal Nocturnal Hemoglobinuria

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) makes patients susceptible to intravascular hemolysis and thrombosis, and it can be life-threatening in stressful situations. Eculizumab, a humanized monoclonal antibody that inhibits the complement protein C5, has been evaluated as a novel therapy for PNH. We herein describe the case of a 59-year-old Japanese woman with classic PNH, who had been successfully treated with eculizumab, but who later developed acute cholecystitis/cholangitis from gallstones. Although the severe obstructive jaundice requiring endoscopic therapy following cholecystectomy was complicated, critical intravascular hemolysis and thrombosis were not observed. Therefore, utilizing eculizumab during the peri-operative management of PNH patients should be carefully taken into consideration.

Key words: PNH, eculizumab, gallstone, cholecystectomy


Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and life-threatening disorder of acquired hemolytic anemia resulting from the clonal expansion of hematopoietic stem cells with somatic mutations in the phosphatidylinositol glycan-complementation class A (PIG-A) gene. The absence of complement control proteins, such as CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis), results in intravascular hemolysis. The clinical manifestations are characterized by a triad of intravascular hemolysis, venous thrombosis, and cytopenias (1). Such cytopenia is caused by bone marrow failure, and some patients may present with aplastic anemia (AA). Depending on whether the clinical manifestation is dominated by hemolysis or by hematopoietic insufficiency, the diagnosis has been proposed to be divided into two categories; classic PNH and PNH/AA syndrome (2).

Stressful situations can provoke hemolytic crisis and thrombosis, which thus renders the management of PNH patients difficult. Drug therapies, such as steroid and androgen therapies, constitute the conventional management, but they only afford the suppression of hemolysis and the improvement of hematopoiesis, and also remain controversial in regard to their effectiveness (3, 4). To date, there is no curative treatment for patients with PNH, except for allogeneic bone marrow transplantation.

Eculizumab, approved in 2007 by the US Food and Drug Administration, is a humanized monoclonal antibody that binds to the complement protein C5 and prevents complement-mediated hemolysis via inhibition of the terminal complement cascade (5). This novel drug has been shown to reduce hemolysis and stabilize hemoglobin levels, thus resulting in a decrease in transfusion requirements in PNH patients (6). Moreover, eculizumab also protects against the complications of hemolytic PNH, such as a deteriorating renal function, pulmonary hypertension, and throm-
boembolism, and thereby contributes to an improvement of survival for such patients (7).

In this case report, we present our experience with the use of eculizumab in a patient who had PNH with concomitant complicated gallstone disease. The hematological stress brought about by cholecystitis/cholangitis with severe jaundice was successfully treated, and open cholecystectomy was performed without inducing a critical exacerbation of intravascular hemolysis and venous thrombosis. Therefore, eculizumab prevented the hemolytic crisis predicted to be induced by obstructive jaundice, and its use should therefore be considered for all PHN patients, especially when surgical intervention is anticipated.

Case Report

A 59-year-old Japanese woman with generalized fatigue was referred to our hematology department in June 2010. She had been diagnosed with classic PNH and followed-up for 20 years at another hospital. Recurrent hemolytic episodes requiring regular blood transfusions (several times per year) without thrombotic complications were noted in her medical history. A physical examination revealed mild pallor but no jaundice. The hematological and laboratory findings were as follows: WBC 11,600/μL (myelocytes 2.0%, metamyelocytes 1.0%, basophils 1.0%, neutrophils 83.0%, monocytes 5.0%, lymphocytes 8.0%), Hb 9.2 g/dL, reticulocytes 18.9×10⁴/μL, Plt 25.2×10⁴/μL, LDH 1,727 IU/L (normal ranging: 115-217), haptoglobin <9 mg/dL, total bilirubin 2.4 mg/dL, and indirect bilirubin 2.0 mg/dL. The findings of direct and indirect Coombs tests were both negative. No abnormalities in the coagulation test were observed, including a fibrin/fibrinogen degradation product (FDP) <5 μg/mL and a D-dimer level <1 μg/mL. The bone marrow biopsy result was normocellular with increased erythropoiesis. The cytogenetic analysis showed a normal karyotype. A flow cytometric analysis of the peripheral blood showed decreased percentages of CD55- and CD59-negative erythrocytes (89.2% and 88.9%, respectively). Abdominal X-ray revealed the existence of gallstones. We diagnosed the patient with classic PNH, and initiated eculizumab treatment after the discontinuation of her previous therapy, which included steroids and cyclosporine A (Figure A).

After the administration of the meningococcal vaccine, eculizumab was initiated at a dose of 600 mg intravenously every 7 days for 4 weeks, and then was increased to 900 mg every 14 days. The intravenous hemolysis was quickly suppressed, and the CH50 value decreased to an undetectable level after the therapy (LDH 3322→312) and blood transfusions were no longer necessary. Although the patient’s clinical course was stable during the eculizumab therapy, after about 14 months, she was admitted to our hospital with acute abdominal pain and generalized jaundice without microscopic hemoglobinuria. Her total bilirubin increased, up to 40.8 mg/dL (direct bilirubin 32.8 mg/dL). She was diagnosed with acute cholecystitis and cholangitis.

On the day of admission, eculizumab was administered four days before the scheduled date, because we were concerned about a potential exacerbation of intravascular hemolysis due to this stressful event. She was treated with antibiotics, and the stones in the common bile duct were removed by endoscopic retrograde biliary drainage (ERBD) and endoscopic sphincterotomy (EST). Despite our concerns that critical intravascular hemolysis and thrombosis could be provoked by this stressful situation, no significant elevations of the values of LDH and D-dimer were observed during the peri-operative period (Figure B). The patient thereafter safely underwent open cholecystectomy with a blood loss of 150 mL. Several red blood cell (RBC) transfusions (total of 20 units) were required, however, no apparent macroscopic hemoglobinuria was observed. The isolated gallstones consisted of a combination of cholesterol and bile salts.

Discussion

The hemolytic episodes in PNH can be provoked by a wide variety of events, including infections (even minor ones), surgery, iron supplementation, vaccinations, and menstruation (8, 9). Our case required EST, ERBD, and open cholecystectomy to treat her gallbladder disease; hence, she was at risk of developing hemolytic crisis as a result of bacterial infection, severe obstructive jaundice, and surgery. An increase in the level of complement proteins, which worsens hemolysis, has been reported to occur following anesthesia, surgery, and various inflammatory conditions (10). The anesthetic management could be harmful for PNH patients, and cardiac arrest due to a hemolytic episode during the induction of anesthesia has been reported (11). Previous reports have also recommended various types of peri-operative management for PNH patients, including the prophylactic administration of antibiotics and granulocyte colony-stimulating factor (G-CSF) to reduce the risk of infection, preoperative transfusion to attain the normal hemoglobin level for prevention of hemolysis by reduction of glycosylphosphatidylinositol (GPI)-deficient erythrocytes, adequate fluid administration with diuretics to prevent renal complications, and thromboprophylaxis (3). Matsuda et al. reported the case of a PNH patient with obstructive jaundice caused by gallstones, who manifested the transient exacerbation of hemolysis during the post-operative period, and they recommended the use of sufficient white cell-depleted red blood cell transfusion (12). In our case, several RBC transfusions in the peri-operative period thus appear to have contributed to the safe management of the patient, while also preventing any exacerbation of hemolysis. While these management are mainly prophylactic approaches, the disease-oriented treatment using eculizumab could therefore be promising for the peri-operative management.

Because it generally takes several weeks for eculizumab to reach a steady state blood concentration after the start of therapy, we recommend initiating this therapy at least a month before surgery, especially in elective situations.

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Figure. (A) The response to eculizumab therapy in a patient with PNH who underwent open cholecystectomy. (B) We focused on the peri-operative clinical course. Large and small triangles indicate transfusion with four units and two units of red blood cells, respectively. CyA: cyclosporine A, PSL: prednisolone.

Singer et al. reported the successful management of a patient who underwent liver transplantation while receiving eculizumab (13). However, even in the era of eculizumab, there are few reports about its efficacy and safety during the peri-operative period.

Our case required several RBC transfusions during the peri-operative period, but did not experience an exacerbation of her intravascular hemolysis. Because hemolytic exacerbation is not limited to the intravascular hemolysis inhibited by eculizumab, extravascular hemolysis could also have developed, in addition to anemia, due to inflammation induced by the cholecystitis/cholangitis. In fact, the decrease in the
hemoglobin level was correlated with the levels of CRP during the peri-operative period, which thus implies that there was exacerbation of anemia due to inflammation (Figure B). A recent study has shown that many of the eculizumab-treated patients become positive for the direct antiglobulin test against C3d (14). Although our case was negative for the direct antiglobulin test against C3d after the operation, despite eculizumab treatment, we found a mild elevation of lactate dehydrogenase (LDH) level during the peri-operative period, possibly caused by extravascular hemolysis (Figure B).

In a retrospective study, the risk of venous thrombosis was found to be related to the large PNH clones (PNH granulocytes >50%); wherein the 10-year risk of thrombosis was 44.0% compared to 5.8% in patients with small clones (15). Our case did not require anti-coagulation therapy despite high percentages of CD55- and CD59-negative clonal erythrocytes (approximately 90%). Because eculizumab has been reported to protect against thromboembolism (16), thrombotic events may have been reduced. Although patients receiving eculizumab have been reported to have an increased susceptibility to bacterial infection from encapsulated organisms, such as meningococcus (17), the acute cholecystitis and cholangitis in our case could be safely managed with antibiotics. Some reports have also shown the safe management with eculizumab even in immunocompromised hosts (13, 18). In fact, a previous study has reported that infections were not more common in patients who received eculizumab than in those who received a placebo (17). Therefore, there may not be a significantly increased risk of bacterial infection due to the decrease of C5 in patients receiving eculizumab therapy, except for those who manifest symptoms of meningitis.

In conclusion, we herein demonstrated the utility and safety of eculizumab treatment in the management of acute cholecystitis/cholangitis and during the peri-operative period for a PNH patient mainly demonstrating intravascular hemolysis. When endoscopic intervention and cholecystectomy are indicated for patients with PNH, eculizumab treatment should therefore be taken into consideration as part of the peri-operative management.

The authors state that they have no Conflict of Interest (COI).

References