



Case Report

A Safety Management Case of Laparoscopic Colectomy in a Patient With Paroxysmal Nocturnal Hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria is a rare and life-threatening disorder of acquired hemolytic anemia. Surgery is one of the major clinical situations that trigger hemolytic attack. Eculizumab is a humanized monoclonal antibody that binds the complement protein C5 and prevents complement-mediated hemolysis via inhibition of the terminal complement cascade. A 76-year-old woman received a diagnosis of ascending colon cancer during the search for the cause of right lower abdominal pain. She had received a diagnosis of paroxysmal nocturnal hemoglobinuria and been followed for 26 years at our hospital. We planned to start eculizumab for perioperative management in order to reduce the risk of the patient developing hemolytic crisis as a result of surgery. We administered 600 mg of eculizumab on the 15th, 8th, and 1st preoperative days. The levels of serum complement and lactate dehydrogenase decreased with the first administration of eculizumab. Laparoscopic right hemicolectomy was performed successfully. The patient had good postoperative progress. We administered 600 mg of eculizumab on the 6th postoperative day and 900 mg of eculizumab on the 13th postoperative day. She was discharged from hospital on the 16th postoperative day. We started use of eculizumab before surgery for safety in the management of the operation and during the perioperative period. When we enforce the elective operation for patients with paroxysmal nocturnal hemoglobinuria who do not start treatment of eculizumab, we recommend the use of eculizumab for perioperative management of patients with paroxysmal nocturnal hemoglobinuria.

Key words: PNH – Eculizumab – Surgery – Colon cancer

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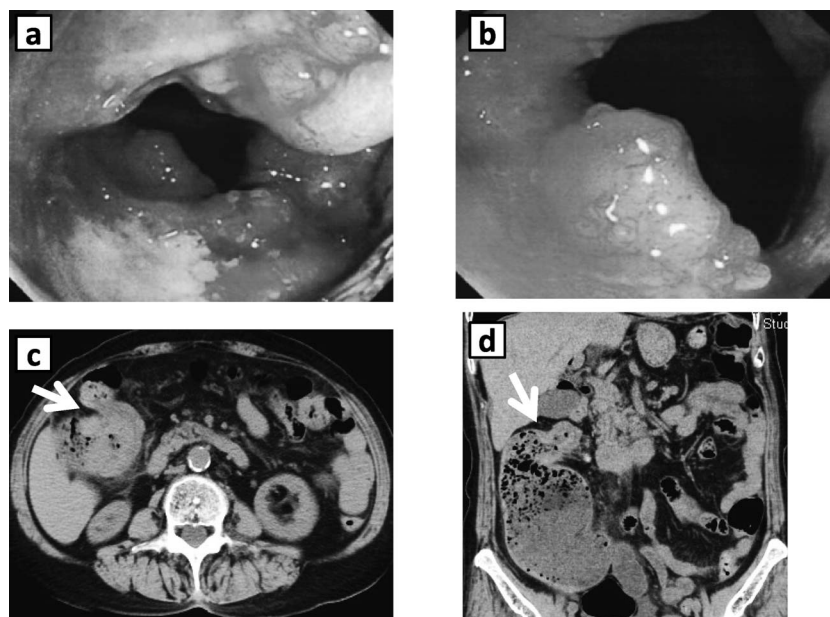


Fig. 1 (a and b) Colonoscopic examination reveals advanced colon cancer. (c and d) Abdominal computed tomography of a tumor of the ascending colon (white arrows).

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and life-threatening disorder of acquired hemolytic anemia.¹ PNH is caused by the clonal expansion of hematopoietic stem cells with somatic mutations in the gene encoding phosphatidylinositol glycan–complementation class A, which is necessary for the synthesis of glycosylphosphatidylinositol. The absence of the glycosylphosphatidylinositol-anchored complement inhibitory proteins CD55 and CD59 on the surface of red blood cells makes them susceptible to complement-mediated lysis and intravascular haemolysis.^{2,3} Complement cascade activation is known to be triggered by a wide variety of events, including infection, trauma, vaccination, menstruation, pregnancy, and surgery.^{4–8}

Eculizumab, approved in 2007 by the US Food and Drug Administration, is a humanized monoclonal antibody that binds to the complement protein C5.^{9,10} Eculizumab inhibits the terminal complement cascade, preventing complement-mediated haemolysis.¹¹ Eculizumab has been shown to be highly effective in reducing anemia, fatigue, transfusion requirements, renal impairment, pulmonary hypertension, and the risk of severe thromboembolic events, ultimately resulting in improved quality of life and survival.^{12–17} However, information regarding the prevention of hemolysis in perioperative management has been limited.

In this case report, we present the clinical course of a patient with PNH complicated by ascending colon cancer that required laparoscopic right hemicolectomy.^{18,19} We describe the inhibition of surgery-

triggered hemolysis via the use of eculizumab. We recommend the use of eculizumab for the perioperative management of patients with PNH.

Case Report

A 76-year-old woman went to another hospital with the main complaint of right lower abdominal pain. She had received a diagnosis of PNH and had been followed for 26 years at our hospital. She had been treated with oral corticosteroids. She received a diagnosis of ascending colon cancer (Fig. 1) during the search for the cause of her right lower abdominal pain. She was transferred to our hospital for the operation. Laboratory data on admission were as follows: white blood cell count, 4820/ μ L; hemoglobin, 8.5 g/dL; platelets, 17.4×10^4 / μ L; lactate dehydrogenase, 841 U/L; blood urea nitrogen, 17 mg/dL; creatinine, 1.08 mg/dL; c-reactive protein, 0.17 mg/dL; and serum complement, 61.1 U/mL. We decided that perioperative management was necessary to reduce the risk of the patient developing hemolytic crisis as a result of surgery.

Eculizumab is generally administered intravenously at a dose of 600 mg weekly for the first 4 weeks, then 900 mg every other week starting on week 5. We planned to administer eculizumab 3 times before the operation, in accordance with our standard protocol: 600 mg of eculizumab was given on the 15th, 8th, and 1st preoperative days. The levels of serum complement and lactate dehydroge-

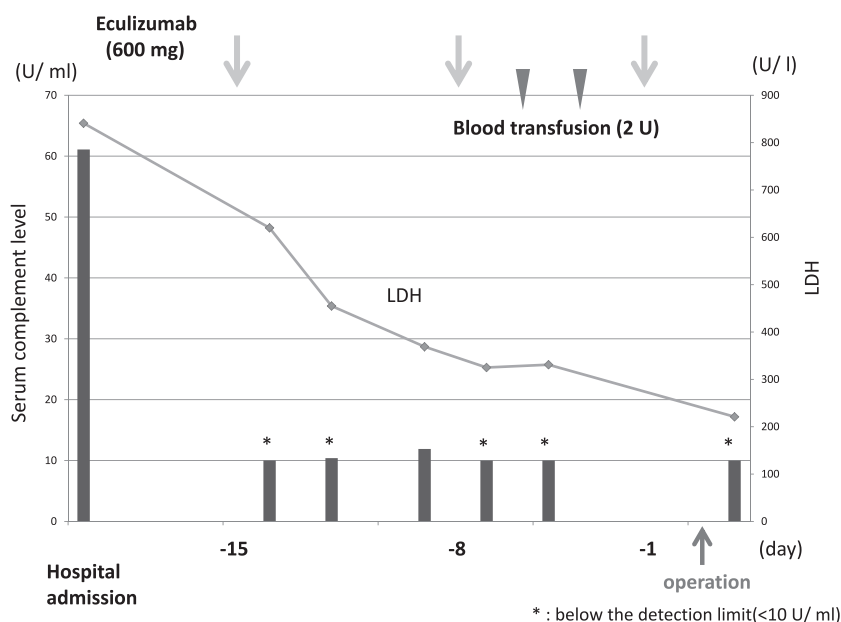


Fig. 2 The preoperative clinical course.

nase decreased with the first administration of eculizumab and remained low.

Before the operation, we transfused 2 U of red blood cells on the fifth and third preoperative days (Fig. 2). Laparoscopic right hemicolectomy was performed successfully with a blood loss of 100 mL under general anesthesia, without any significant complications. The histopathologic diagnosis was moderately differentiated tubular adenocarcinoma. The final stage was T3N1aM0 stage IIIB according to the guidelines of the Union for International Cancer Control (Fig. 3).

The patient displayed good postoperative progress. We administered 600 mg of eculizumab on the 6th postoperative day and then 900 mg of eculizumab on the 13th postoperative day. The patient was discharged from the hospital on the 16th postoperative day. We administered 900 mg of eculizumab every other week at her outpatient visits.

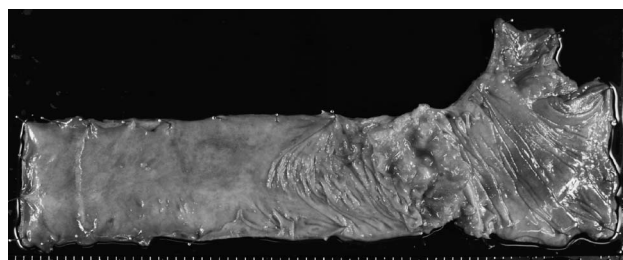


Fig. 3 Macroscopic findings of cancer in the resected specimen of the ascending colon.

Discussion

Hemolytic episodes in PNH can be provoked by stressful situations, including infection, trauma, pregnancy, and surgery.⁴⁻⁸ Surgery is a major risk factor for hemolytic crisis through complement activation. Previous reports recommended various types of perioperative management. Preoperative transfusion of red blood cells increases hemoglobin levels and prevents hemolysis by reducing the presence of glycosylphosphatidylinositol-deficient red blood cells.^{8,20,21} Prophylactic administration of antibiotics and granulocyte colony-stimulating factor reduces the risk of infection, especially in cases of bone marrow aplasia in addition to PNH.²⁰ Low-molecular weight heparin was previously recommended in high-risk situations to prevent thrombosis.⁴ Both hemolytic crisis and symptoms of steroid withdrawal are avoided because patients receive long-term steroid therapy.²² Successful surgical management without eculizumab has been reported, but we recommend the use of eculizumab for perioperative management because of its additional safety benefits. We started the use of eculizumab before surgery for safety in the management of the operation and during the perioperative period. When enforcing the elective operation for patients with PNH who do not start treatment of eculizumab, the administration of eculizumab should be recommended to improve perioperative safety, such as through reduction of postoperative complications.

Table 1 Case reports of the use of eculizumab for the perioperative period

No.	Source, y	Age, y	Sex	Diagnosis	Operation
1	Singer <i>et al.</i> ²³ 2009	32	Male	Budd-Chiari syndrome	Liver transplantation
2	Van Bijnen <i>et al.</i> ²⁴ 2011	70	Male	Endocarditis	Cardiopulmonary bypass
3	Kawano <i>et al.</i> ²⁵ 2012	60	Female	Cholecystitis	Cholecystectomy
4	Kurita <i>et al.</i> ²⁶ 2013	64	Male	Gastric cancer	Distal gastrectomy
5	Our case	76	Female	Colon cancer	Right hemicolectomy

Four reports have addressed the use of eculizumab during the perioperative period (Table 1). Singer *et al.*²³, Van Bijnen *et al.*²⁴ and Kawano *et al.*²⁵ reported the successful management of patients who underwent liver transplantation, cardiopulmonary bypass, and cholecystectomy, respectively, during maintenance treatment with eculizumab. Kurita *et al.*²⁶ reported the successful management of a patient who underwent distal gastrectomy with the temporary use of eculizumab (600 mg, once a week \times 4 times) during the perioperative period. Limited administration of eculizumab could be an option for PNH patients with transient and anticipated high risks.

In conclusion, this case report demonstrates the utility and safety of eculizumab treatment for perioperative management of PNH. Eculizumab treatment should be taken into consideration as a main part of the perioperative management of these patients.

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