Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9151-17
Intern Med 57: 127-130, 2018
http://internmed.jp

【 CASE REPORT 】

Severe Infection of *Pseudomonas aeruginosa* during Eculizumab Therapy for Paroxysmal Nocturnal Hemoglobinuria

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Abstract:
Eculizumab is the complement inhibitor administered to ameliorate intravascular hemolysis in paroxysmal nocturnal hemoglobinuria. Whether or not the inhibitory mechanism may also increase the susceptibility to non-*Neisserial* infection is unclear. A 73-year old woman presented with bacteremia, cholecystitis and liver abscess with *Pseudomonas aeruginosa*. Although she had been neutropenic for 21 years, she had no history of severe infection before eculizumab had been administered. The infection with *P. aeruginosa* was successfully controlled with antibiotics, granulocyte colony-stimulating factor and cholecystectomy. The present case might be representative of less common bacterial infections than *Neisseria* spp. among patients treated with eculizumab.

Key words: eculizumab, *Pseudomonas aeruginosa*, paroxysmal nocturnal hemoglobinuria, anti-complement therapy

(Intern Med 57: 127-130, 2018)
(DOI: 10.2169/internalmedicine.9151-17)

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) originates from the nonmalignant clonal expansion of hematopoietic progenitor cells that harbor an acquired somatic mutation of PIG-A (1). The progeny of the mutated precursors, lacking the glycosylphosphatidylinositol-anchored complement regulatory proteins CD55 and CD59, are vulnerable to membrane attack complex (MAC), the final product of complement cascades, which lead to intravascular hemolysis in affected individuals (1, 2). Eculizumab is a recombinant, humanized monoclonal antibody that blocks complement factor 5, ultimately resulting in the suppression of MAC formation (3-5). By inhibiting of the complement-mediated cell destruction, eculizumab may reduce hemolysis and improve anemia, the renal function, the patient survival and the quality of life (2, 6). Since the MAC also plays a key effector role in extracellular killing in pyogenic infections, an individual on eculizumab therapy has a higher risk of developing potentially life-threatening infections with encapsulated organisms, particularly with *Neisseria* spp (2, 7).

Eculizumab has been considered a major breakthrough in the understanding and management of complement-mediated pathology, and it represents a number of other promising therapeutic approaches to the complement system now under development (3). However, less is known about the association of eculizumab and other infections aside from *N. meningitides* infection (7). Serious infections by other pathogens have been only anecdotally reported, including *P. aeruginosa* (8), *Aspergillus niger* (9), polyomavirus JC (10) and Herpes simplex (11). Among them, Webb et al. reported a case of fatal *P. aeruginosa* bacteremia after eculizumab administration for atypical hemolytic uremic syndrome, implying that other less common therapy-related infectious consequences may have been under-recognized and that further

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Received: March 7, 2017; Accepted: April 26, 2017; Advance Publication by J-STAGE: October 11, 2017
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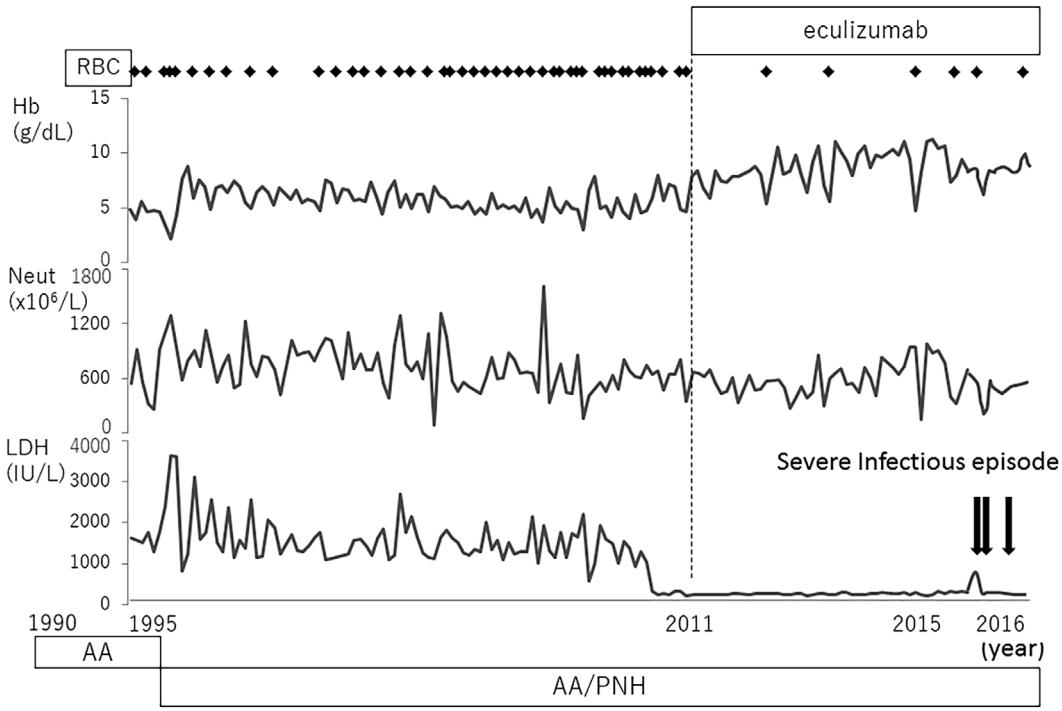

Figure 1. **The levels of neutropenia, anemia and LDH before and after the administration of eculizumab. AA was diagnosed in 1990 and PNH in 1995. Eculizumab was started in 2011. Each dot represents 2 units of RBC transfusion. The LDH level and frequency of transfusion dropped dramatically after the introduction of eculizumab. The neutrophil counts did not change significantly with eculizumab. The arrows represent the three consecutive infectious episodes described in this report. LDH: lactate dehydrogenase, PNH: paroxysmal nocturnal hemoglobinuria, RBC: red blood cell, Hb: hemoglobin, Neut: neutrophil**

studies should be performed (8).

We herein report a case of invasive infection with *P. aeruginosa* during eculizumab therapy for PNH.

Case Report

A 73-year-old woman presented to our hospital because of fatigue and a fever. She had had a 25-year history of AA and had been treated with prednisolone (PSL) and/or metenolone. In the fifth year of the clinical course of AA, PNH was diagnosed based on positive results for a sugar water test, which was later confirmed with flow cytometry that detected 93% of CD55- and CD59-deficient PNH-type red blood cells as of 2005. During the clinical course of PNH, multiple hemolytic episodes as well as bone marrow failure had required the patient to undergo a number of red blood cell transfusions at least every other month to keep her hemoglobin concentration level above 5 g/dL. She did not require any platelet transfusions. Although the neutrophil counts ranged between about 500 and 700×10^6/L, she did not develop any serious infections requiring hospitalization. In 2011, eculizumab therapy was started for PNH, which dramatically reduced the number of hemolytic episodes. PSL, which had been prescribed to control the hemolysis, was withdrawn by 2012. Her neutrophil counts did not change significantly before or after the introduction of eculizumab (Fig. 1). Meningococcal vaccine was administered before and 3 years after the introduction of eculizumab.

The patient started to complain of nasal discharge, cough, a fever, right flank pain and general fatigue 10 days prior to admission. Red blood cell transfusion for anemia and amoxicillin for possible upper respiratory tract infection did not improve her fever, and she presented to our hospital in November 2015. At presentation, she had a fever of 40℃, heart rate 133 beats per minute, blood pressure 75/51 mmHg and respiratory rate 38 times per minute. She did not have any signs or symptoms in the abdomen at the presentation. Her laboratory data showed white blood cell counts 440×10^6/L (neutrophils 5%, metamyelocytes 1%, lymphocytes 57%, monocytes 37%), hemoglobin 4.8 g/dL, platelets 64×10^9/L, T-Bil 4.27 mg/dL, D-Bil 1.88 mg/dL, lactate dehydrogenase (LDH) 355 U/L (the reference range of normal 120-230 U/L), haptoglobin 43 mg/dL, C3 61 mg/dL, C4 13.4 mg/dL and CH50<4 U/mL. With the blood culture yielding *P. aeruginosa*, a diagnosis of septic shock was made. The detected strain of *P. aeruginosa* was sensitive to cefepime and meropenem. Non-enhanced computed tomography (CT) of the chest and upper abdomen showed no signs of focal infections, including cholecystitis. The sepsis was brought under control after the administration of antibiotics including cefepime and meropenem, intravenous immunoglobulin, granulocyte-colony stimulating factor (G-CSF) and catecho-

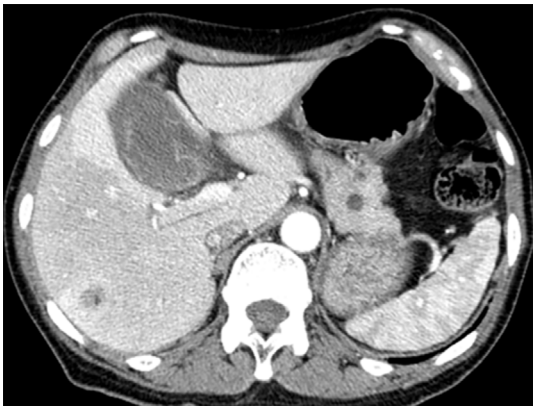

Figure 2. **Contrast-enhanced computed tomography (CT) in the abdomen on the second admission. The gallbladder wall became ill-defined with poor enhancement. Multiple mass lesions with peripheral enhancement were detected in the liver.**

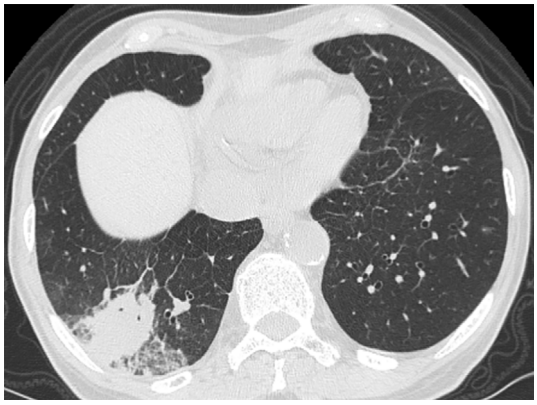

Figure 3. **Non-contrast CT in the lungs on the third admission. Infiltrative shadow was observed in the right inferior lobe.**

lamine. Her general condition was stabilized, and she was discharged from the hospital 14 days after admission.

A week after the discharge, however, she presented to an emergency room because of pain in the right upper abdomen. An enhanced CT scan of the abdomen revealed gangrenous cholecystitis and multiple hepatic abscesses (Fig. 2). Laparoscopic cholecystectomy was performed, and the bile culture was found to be positive for *P. aeruginosa.* The strains still showed sensitivity to cefepime and meropenem *in vitro*. Meropenem was re-started with G-CSF for neutropenia. Her liver abscess disappeared after two-month administration of meropenem or cefepime, alternatively.

The patient presented again with a sustained fever and was admitted to our hospital in February 2016. A non-enhanced CT scan of the chest revealed infiltration in the inferior lobe of the right lung (Fig. 3). The laboratory data showed a white blood cell count of 740×10^{6}/L (neutrophils 40%, metamyelocytes 1%, lymphocytes 49%, monocytes 9%), hemoglobin 6.2 g/dL, platelets 40×10^{9}/L, T-Bil 2.91 mg/dL, LDH 222 U/L, haptoglobin 60 mg/dL, C3 100 mg/dL, C4 22.4 mg/dL, CH50 7.6 U/mL, IgG 1,645 mg/dL, IgA 230 mg/dL and IgM 55 mg/dL. No pathogens were cultured from the blood, sputum or bronchoalveolar lavage fluid. Wide-spectrum antibiotics and short-term hydrocortisone improved her pneumonia. The patient remained free from another infectious episode for the next 12 months.

Discussion

The inhibition of complement at C5 by eculizumab is a well-known risk factor for developing life-threatening infections with encapsulated organisms, particularly *N. meningitides* and *N. gonorrhoeae* (2, 7). Although terminal complement deficiencies may jeopardize immune systems against a variety of exogenous pathogens other than *Neisseria* spp, less is known about the association of eculizumab with other infections, and only anecdotal reports like the present case and small case series have been documented (7, 12). In the SHEPHERD study, a multinational, single-arm, safety and efficacy study of eculizumab for PNH, 6 of the 97 enrolled patients reportedly developed severe infection, including pyrexia, cholangitis, endometritis, pyelonephritis and viral infection, although their causal relationships were not definite (4). Ninomiya et al. found that eculizumab therapies were associated with severe non-*Neisserial* infections, including pneumonia (0.9%), sepsis (1.3%), Herpes zoster infection (0.3%) and infection with unknown pathogen (0.6%) among 319 patients enrolled in a post-marketing surveillance (13). The present case, which exhibited bacteremia, cholecystitis and liver abscess due to *P. aeruginosa* and pneumonia with unknown bacteria consecutively, may represent one of the less common, non-*Neisserial*, severe infectious adverse events associated with eculizumab.

Underlying medical conditions may also be attributable to the increased susceptibility of recurrent infectious episodes during eculizumab therapy like in the present case. Fig. 1 illustrates the sustained neutropenia, which might have increased the risk of opportunistic infections, during the clinical course of aplastic anemia in the present case. Although the level of neutropenia had fluctuated, it did not seem to change significantly after the diagnosis of PNH and after the introduction of eculizumab, implying that there was more to the increased risk of infection than the neutropenia alone. According to Younger et al., complement-deficient mice were more susceptible to *P. aeruginosa* infection than intact mice, although they harbored a normal neutrophil recruitment capacity (14). Their results may be in accordance with our observation that complement blockage might be associated with the repeated *P. aeruginosa* infection noted in the present case. Glucocorticoid administration may also be involved in the repeated infections, though PSL had been withdrawn three years earlier in the present case. Previous hospitalization and exposure to antibiotics in the past might have led to a carrier state of *P. aeruginosa* as well. These multiple risk factors, including eculizumab administration, might have played accumulating roles in triggering repeated infections, as in the previous report (8).

Recently, new complement-mediated medications other than eculizumab have been under development, such as C1 esterase inhibitor for angioedema or C3 inhibitors for PNH (3). Because complement inhibition is expected to lead to an increased susceptibility to infection, as represented by eculizumab, the accumulation of more case reports or series involving less common infectious complications associated with eculizumab will be required in order to clarify the safety profiles of eculizumab itself as well as other anti-complement medications in the pipeline.

In summary, this may be a representative case of less common infectious complications of complement-inhibiting therapies, including eculizumab.

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

References

1. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood **106**: 3699-3709, 2005.
2. Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood **113**: 6522-6527, 2009.
3. Ricklin D, Lambris JD. Complement-targeted therapeutics. Nat Biotechnol **25**: 1265-1275, 2007.
4. Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood **111**: 1840-1847, 2008.
5. Hillmen PYN, Schubert J, Brodsky RA, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med **355**: 11, 2006.
6. Kelly RJ, Hill A, Arnold LM, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood **117**: 6786-6792, 2011.
7. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. Curr Opin Infect Dis **29**: 319-329, 2016.
8. Webb BJ, Healy R, Child B, Majers J, Anand S, Gouw L. Recurrent infection with *Pseudomonas aeruginosa* during eculizumab therapy in an allogeneic hematopoietic stem cell transplant recipient. Transpl Infect Dis **18**: 312-314, 2016.
9. Vellanki VS, Bargman JM. *Aspergillus niger* peritonitis in a peritoneal dialysis patient treated with eculizumab. Ren Fail **36**: 631-633, 2014.
10. Gomez-Cibeira E, Ivanovic-Barbeito Y, Gutierrez-Martinez E, et al. Eculizumab-related progressive multifocal leukoencephalopathy. Neurology **86**: 399-400, 2016.
11. Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. Lancet **373**: 759-767, 2009.
12. Patir P, Isik Y, Turk Y, et al. Necrotizing fasciitis in paroxysmal nocturnal hemoglobinuria. Case Rep Hematol **2015**: 908087, 2015.
13. Ninomiya H, Obara N, Chiba S, et al. Interim analysis of post-marketing surveillance of eculizumab for paroxysmal nocturnal hemoglobinuria in Japan. Int J Hematol **104**: 548-558, 2016.
14. Younger JG, Shankar-Sinha S, Mickiewicz M, et al. Murine complement interactions with *Pseudomonas aeruginosa* and their consequences during pneumonia. Am J Respir Cell Mol Biol **29**: 432-438, 2003.