


## CASE REPORT

# Preoperative administration of eculizumab to prevent surgery-triggered hemolysis during cesarean section with paroxysmal nocturnal hemoglobinuria

Dongping Li<sup>1</sup> | Liangcheng Wang<sup>1</sup>  | Isao Horiuchi<sup>1</sup> | Shun-ichi Kimura<sup>2</sup> | Kenro Chikazawa<sup>1</sup> | Azusa Kimura<sup>1</sup> | Shigetane Sasaki<sup>1</sup> | Tomoyuki Kuwata<sup>1</sup> | Kenjiro Takagi<sup>1</sup>

<sup>1</sup>Perinatal and Maternal Center of Saitama Medical Center, Jichi Medical University, Saitama, Japan

<sup>2</sup>Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan

**Correspondence:** Liangcheng Wang, Perinatal and Maternal Center of Saitama Medical Center, Jichi Medical University, 1-847, Amanuma-cho, Omiya-ku, Saitama 330-8503, Japan (kksesc@gmail.com).

## Key Clinical message

Eculizumab in pregnancy has been reported to be effective in improving outcomes in patients with paroxysmal nocturnal hemoglobinuria. However, a cesarean section may result in surgery-triggered hemolysis. An additional dose of eculizumab just prior to delivery is an appropriate choice to prevent postoperative hemolysis.

## KEYWORDS

cesarean section, eculizumab, hemolysis, paroxysmal nocturnal hemoglobinuria

## 1 | INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hemolysis disorder that results from uncontrolled complement system activation and causes hemolytic anemia and marrow failure. Infection and thrombosis are also severe complications of PNH, which can be life-threatening. Administration of eculizumab, a complement inhibitor of C5, during pregnancy has been reported useful in improving maternal and fetal outcomes in patients with PNH.<sup>1</sup> However, the need for peripartum dose adjustment is rarely discussed. We herein report a case of a patient with PNH who underwent two cesarean deliveries under eculizumab treatment and discuss the necessity of eculizumab peripartum dose adjustment.

## 2 | CASE PRESENTATION

A 34-year-old primipara woman was diagnosed when she was 18 years with PNH, which started with symptom of hematuria and anemia. Anemia was under control by iron agents

without transfusion. There was no episode of thrombosis. However, she was diagnosed with asymptomatic primary biliary cholangitis at 33 years and received her first eculizumab treatment for hemolysis at 34 years, which started with a loading dose of 600 mg once a week and was subsequently increased to 900 mg every 2 weeks. The response to eculizumab was good. Three months later, she was found to be pregnant. Administration of eculizumab, 900 mg every 2 weeks, was continued, and she had no episode of hemolysis during pregnancy. At gestational week 39, she was hospitalized due to fetal growth restriction (FGR). Labor was induced by oxytocin at week of 40, but an emergency cesarean section was required due to abnormal fetal heart rate (late deceleration). A healthy 2775-g male infant with Apgar score of 7/9 at 1/5 minutes was delivered. On postoperative day 5, the patient's C-reactive protein (CRP) increased to 10.2 mg/dL and her lactate dehydrogenase (LDH) increased to 637 IU/L, which revealed hemolysis. Thus, the patient was administered 5000 units of heparin subcutaneously twice daily for 6 weeks and 900 mg of eculizumab every 2 weeks. After the treatment, hemolysis was controlled. Two years later, a

second pregnancy was detected during eculizumab treatment. The pregnancy course was uneventful, with no hemolysis observed. With the patient's history of postoperative hemolysis, preoperative administration of eculizumab was given 1 day just before her cesarean section. At gestational week 37, a cesarean section was performed and a healthy female baby with Apgar score of 8/9 was delivered. Subsequently, eculizumab and 6 weeks of subcutaneous heparin were administered postpartum; no evidence of hemolysis was found (Figure 1).

### 3 | DISCUSSION

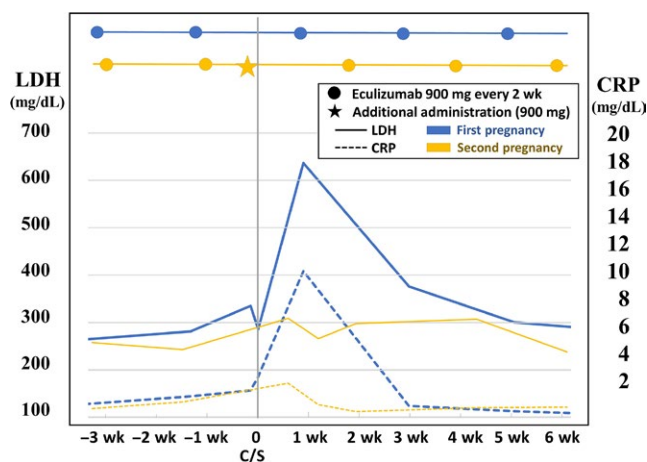
Eculizumab is a monoclonal antibody that binds to complement C5, inhibiting the formation of the C5-9 terminal complement complex that attacks the membrane of red blood cells. Eculizumab has a half-life of 4-21 days<sup>2</sup> and is metabolized into small peptides and amino acids by lysosomal enzymes. Nakayama et al<sup>3</sup> retrospectively analyzed 763 doses in 14 patients with PNH and concluded that prolonged dosing intervals of 17 days or more may be associated with the development of breakthrough hemolysis (LDH >1000 U/L). A 50% hemolytic complement (CH50) activity and evaluated LDH levels are strongly associated with circulating free eculizumab.<sup>4</sup> These parameters can also predict postoperative infection and hemolysis. LDH is one of the easily measured parameters when monitoring patients with PNH on eculizumab.<sup>3,5</sup> The shortened interval or increased dosage is recommended if hemolysis occurred.<sup>4</sup>

Operative invasion, trauma, and anesthesia are factors that activate the complement system,<sup>6</sup> resulting in surgery-triggered hemolysis. Postoperative complement system activation is also associated with inflammatory response<sup>7</sup> as well as alternative pathway through bacterial invasion. Therefore, postoperative complement system activation is a

major concern during postoperative management of patients with PNH. Successful preoperative administration of eculizumab to prevent postoperative hemolysis has been reported in other surgeries, for example, in cardiopulmonary bypass.<sup>8</sup> In obstetrics, eculizumab given before cesarean section has been described in a patient with severe antiphospholipid syndrome.<sup>9</sup> However, very few similar discussions in obstetrics are reported.

Previously, before eculizumab was available, pregnancy was not recommended in patients with PNH. The mortality rate of pregnant women with PNH is 8%-20%, and hepatic venous thrombosis (Budd-Chiari syndrome) was known as a major cause of maternal death.<sup>10</sup> In addition, cases of hemolytic crisis (28%), thrombosis (14%), and hemorrhage (mainly cerebral, 14%) are highly common in pregnancy. The rate of fetal wastage is as high as 30%, mostly due to abortion.<sup>10</sup> After eculizumab became available, maternal and fetal prognosis has improved. Kelly et al<sup>1</sup> investigated 61 pregnant women with PNH from 31 institutes in 9 countries and observed that the maternal survival rate was 100%, with live birth rate of 92%, when eculizumab was given. Even with a preterm labor rate as high as 29% and the risk of preeclampsia and FGR, which are the most common reasons for requiring termination, the long-term prognosis of the offspring is very good.<sup>1</sup> In terms of effects on the fetus, despite the presence of eculizumab in umbilical blood,<sup>11</sup> no suppression of complement system was found in newborn babies.<sup>12</sup> Therefore, eculizumab administration is considered safe during pregnancy.

An increase in soluble fms-like tyrosine kinase 1 (sFLT-1) in maternal serum may account for ischemic placental disease such as HELLP/preeclampsia/FGR,<sup>13,14</sup> and eculizumab administration decreases sFLT-1. Burwick and Feinberg<sup>15</sup> reported a case of severe preeclampsia/HELLP syndrome that was treated with eculizumab, which led to a temporary normalization of the patient's laboratory parameters and to prolongation of gestational from 26 to 29 weeks. Conversely, 50% (11/22) of chronic renal failure patients with PNH had improved symptoms after eculizumab administration.<sup>16</sup> Although eculizumab contributes to the prevention of hemolysis, preeclampsia, and renal failure, it is rapidly metabolized by activated lysosomes as pregnancy progresses. Approximately 54% of patients with PNH need increased dose of eculizumab for the treatment of hemolysis.<sup>1</sup> To date, the appropriate timing to increase eculizumab during pregnancy has not been well discussed. In the present case, we observed that administration of eculizumab 1 day just before cesarean section prevented postoperative hemolysis. Hence, we believe that elective cesarean section should be performed soon after routine eculizumab infusion, or an extra dose to shorten the interval between eculizumab infusion and cesarean section should be considered to help prevent postoperative hemolysis. Further research is required to verify the results observed for our case.



**FIGURE 1** Peripartum LDH and CRP Levels in the First and Second Pregnancies. CRP, C-reactive protein; C/S, cesarean section; LDH, lactate dehydrogenase

## ACKNOWLEDGMENTS

We would like to thank Editage ([www.editage.jp](http://www.editage.jp)) for English language editing.

## CONFLICT OF INTEREST

The authors declare no conflict of interests.

## AUTHORSHIP

LW, DL, AK, SS, and TK: were involved in writing the manuscript. LW, SK, IH, KC, and KT: were involved in the management of the patient.

## ORCID

Liangcheng Wang  <http://orcid.org/0000-0002-7579-0233>

## REFERENCES

- Kelly RJ, Höchsmann B, Szer J, et al. Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2015;373:1032-1039.
- De Latour RP, Fremaux-Bacchi V, Porcher R, et al. Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. *Blood*. 2015;125:775-783.
- Nakayama H, Usuki K, Echizen H, Ogawa R, Orii T. Eculizumab dosing intervals longer than 17 days may be associated with greater risk of breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria. *Biol Pharm Bull*. 2016;39:285-288.
- Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2015;124:2804-2812.
- Sharma R, Keyzner A, Liu J, Bradley T, Allen SL. Successful pregnancy outcome in paroxysmal nocturnal hemoglobinuria (PNH) following escalated eculizumab dosing to control breakthrough hemolysis. *Leuk Res Reports*. 2015;4:36-38.
- Schutte M, DiCamelli R, Murphy P, Sadove M, Gewurz H. Effects of anesthesia, surgery and inflammation upon host defense mechanisms. I. Effects upon the complement system. *Int Arch Allergy Appl Immunol*. 1975;48:706-720.
- Bruins P, te Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation*. 1997;96:3542-3548.
- van Bijnen STA, Vermeer H, Mourisse MJM, de Witte T, van Swieten HA, Muus P. Cardiopulmonary bypass in a patient with classic paroxysmal nocturnal hemoglobinuria during treatment with eculizumab. *Eur J Haematol*. 2011;87:376-378.
- Gustavsen A, Skattum L, Bergseth G, et al. Effect on mother and child of eculizumab given before caesarean section in a patient with severe antiphospholipid syndrome: a case report. *Medicine (Baltimore)*. 2017;96:e6338.
- Bais J, Pel M, von dem Borne A, van der Lelie H. Pregnancy and paroxysmal nocturnal hemoglobinuria. *Eur J Obstet Gynecol Reprod Biol*. 1994;53:211-214.
- Ando Y, Kida M, Saika M, et al. Pregnancy and delivery in a PNH patient treated with eculizumab. *Rinsho Ketsueki*. 2014;55:2288-2293.
- Hallstensen RF, Bergseth G, Foss S, et al. Eculizumab treatment during pregnancy does not affect the complement system activity of the newborn. *Immunobiology*. 2015;220:452-459.
- Herraiz I, Droge LA, Gomez-Montes E, Henrich W, Galindo A, Verlohren S. Characterization of the soluble fms-like tyrosine kinase-1 to placental growth factor ratio in pregnancies complicated by fetal growth restriction. *Obstet Gynecol*. 2014;124:265-273.
- Zeisler H, Llorba E, Chantraine F, et al. Predictive value of the sFlt-1:PIGF ratio in women with suspected preeclampsia. *Obstet Gynecol Surv*. 2016;71:273-274.
- Burwick RM, Feinberg BB. Eculizumab for the treatment of preeclampsia/HELLP syndrome. *Placenta*. 2013;34:201-203.
- Villegas A, Nunez R, Gaya A, et al. Presence of acute and chronic renal failure in patients with paroxysmal nocturnal hemoglobinuria: results of a retrospective analysis from the Spanish PNH Registry. *Ann Hematol*. 2017;96:1727-1733.

**How to cite this article:** Li D, Wang L, Horiuchi I, et al. Preoperative administration of eculizumab to prevent surgery-triggered hemolysis during cesarean section with paroxysmal nocturnal hemoglobinuria. *Clin Case Rep*. 2018;6:1807–1809. <https://doi.org/10.1002/ccr3.1707>