A Successful Planned Pregnancy and Delivery with Eculizumab Maintenance in a Woman with Paroxysmal Nocturnal Hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disorder characterized by complement-mediated hemolysis leading to severe complications, such as life threatening thrombosis. Eculizumab, a humanized anti-C5 monoclonal antibody, has dramatically improved outcomes of patients with PNH. Despite this new revolutionary treatment, clinical information regarding eculizumab use in pregnant women with PNH is limited. A 30-year-old female with PNH underwent acute aggravation of PNH presented with acute kidney injury (AKI) triggered by an infectious event. After the stabilization of AKI with supportive care and later continuous eculizumab use, a planned pregnancy was attempted and achieved because she and her spouse wanted to have a baby. We monitored the patient carefully throughout her pregnancy with 100 mg/day of aspirin and the maintenance of 900 mg of intravenous eculizumab every 2 weeks. She remained stable during pregnancy and a successful delivery was achieved without materno-fetal complication.

Keywords: Hemoglobinuria, paroxysmal; Eculizumab; Pregnancy

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disorder with abnormal stem cell clones. In patients with PNH, acquired mutations occur in the PIGA gene, responsible for the synthesis of the glycosphatidyl inositol (GIP) anchor that attaches proteins to the cell surface [1]. Loss of GIP-linked proteins caused by mutations results in increased sensitivity for cytosis of complements [1]. The characteristic features of PNH include intravascular hemolysis, thrombosis, and cytopenia, causing significant morbidity and mortality [1]. Eculizumab, a humanized monoclonal antibody against complement protein C5, reduces complement-mediated hemolysis and has dramatically improved patient outcomes [2]. Pregnancy in women with PNH has long been considered a relative contraindication due to higher risk of materno-fetal complications [3]. Here, we report on a Korean PNH woman who benefited from eculizumab by achieving a safe planned pregnancy and delivery.

CASE REPORT

A 30-year-old married woman was admitted to the nephrology department in July 2013 because of fever and diarrhea. Three days ago she visited a community hospital and was prescribed antibiotics with the suspicion of pyelonephritis. Despite antibiotic use, symptoms were not improved and acute kidney injury (AKI) developed. She was diagnosed with PNH in 1998 at the hematology department of Gachon University Gil Medical Center and has maintained outpatient department-based surveillance only with iron replacement. Blood cell counts were as follows: hemoglobin 9.7 g/dL, reticulocytes 4.8%, white blood cell 6,860/μL, and platelets 83,000/μL. Biochemistry tests showed total bilirubin 1.7 mg/dL, direct bilirubin 0.54 mg/dL, blood urea nitrogen (BUN) 37.6 mg/dL, creatinine 6.4 mg/dL, and lactate dehydrogenase (LDH) 1,508 U/L (485 U/L for upper normal limit). Coagulation tests including prothrombin time, activated partial thromboplastin time, and D-dimer were all within normal range. Flow cytometry analy-
sis using patient’s peripheral blood showed fluorescent aerolysin-negative granulocytes (Fig. 1A-C) and CD59-deficient red blood cells (Fig. 1D, E), findings consistent with PNH. Kidney biopsy revealed hemosiderin deposit on tubules with positive iron staining, demonstrating acute hemolysis probably caused by PNH. Hemodialysis was initiated since hospital day 5 with 1 mg/kg/day of prednisolone. With four more hemodialysis sessions, BUN and creatinine were decreased to 24.2 mg/dL and 1.4 mg/dL, respectively. She was discharged on day 16 with the planning of eculizumab after the approval of its use in the advance ruling by the Korean National Health Insurance Review and Assessment Service.

Two months later, eculizumab therapy became available. Eculizumab was administered with dosing schedules as previously described: a 600 mg was infused intravenously (i.v.) every 7 days for the first 4 weeks, then a 900 mg was administered at the 5th week, and a 900 mg of eculizumab has been infused every 2 weeks thereafter [2]. After use of eculizumab, she maintained a normalized LDH level and normal renal function. Because she wanted a baby, the risk of pregnancy in the situation was discussed. Based on a few reports on safe pregnancy outcome [2,4,5] and the strong motivation of the couple, a planned pregnancy was attempted and then intrauterine pregnancy (IUP) was confirmed. We recommended anticoagulation with low molecular weight heparin (LMWH); however, only 100 mg/day of aspirin was added because she refused subcutaneous injection of the drug. We observed the patient carefully throughout her pregnancy with 900 mg of i.v. eculizumab every 2 weeks. She remained stable during pregnancy: no episode of breakthrough hemolysis, thrombosis, or re-emergence of AKI was observed. She required no red cell transfusion and maintained ≥100,000/μL of platelet count throughout pregnancy. After regular checkups, she made a successful delivery at 39 weeks and the first day of her IUP. Both mother and baby were healthy and well. Aspirin was discontinued six weeks after the delivery. She has been taking eculizumab so far, with no complication to date (Fig. 2).

**DISCUSSION**

Fieni et al. [6] reviewed 26 published reports from 1970 to 2005, describing pregnancy outcome in 43 women with PNH: the incidence rate of major maternal complications was 16.3% during pregnancy and 39% underwent a preterm delivery with an fetal
death rate of 7.2%. Thrombosis was the most common postpartum maternal complication (18.6%) and three patients died, while two other patients died of infection, overall maternal mortality rate was 11.6% [6]. A French group also retrospectively analyzed 27 pregnancies in 22 women between 1978 and 2008 and reported similar results [7]. Based on the results, women with PNH have usually been discouraged from becoming pregnant. Once pregnant, anticoagulation usually with LMWH has been strongly recommended, particularly postpartum [7].

With the introduction of eculizumab, the obstetric risk needed to be re-evaluated, and now evidences are gathering that pregnancy can be much more safely managed with eculizumab. A questionnaire study on 75 pregnancies in 61 women in Western countries was recently reported [8]. The incidence rate of premature birth (22 births, 29%) was similar to that of reports in the pre-eculizumab era [6,7] but only 3 fetal deaths (4%) were reported [8]. They reported no maternal death. No thrombotic events occurred during pregnancy and two events were reported postpartum. The results show that eculizumab made a significant contribution to safer obstetric outcomes. However, the use of eculizumab itself is not an absolute guarantee of a successful pregnancy, and there should be some considerations even with eculizumab. First, increased transfusion requirement is observed even with eculizumab [8]. Second, risk of thrombotic event during postpartum is still observed even with eculizumab [8]. Therefore, careful monitoring is required during postpartum. Third, pre-emptive increase of the dose and/or the frequency of eculizumab should be considered, especially with the evidence of breakthrough hemolysis [8].

Our patient received low dose aspirin instead of anticoagulation. However, in the literature, most patients received anticoagulation during pregnancy and postpartum [2,4-9] and low dose aspirin cannot substitute anticoagulation in general. In the pre-eculizumab era, several indicators were suggested as risk factors of thrombosis, including the size of PNH clone, age, and prior thrombosis, etc. [10]. It could be re-evaluated in the eculizumab era.

Our case, the first Korean patient on eculizumab followed through pregnancy, demonstrated a very stable maintenance of pregnancy and successful delivery using minimal prophylactic measure in a female patient with lower risk of thrombosis.

REFERENCES


