



Treatment of paroxysmal nocturnal hemoglobinuria in pregnancy with eculizumab: A case report

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease caused by mutations in hematopoietic stem cells leading to pancytopenia and a predisposition for thromboembolic events. In pregnancy, these manifestations can be amplified, leading to increased neonatal and maternal morbidity and mortality. Although data are limited, eculizumab has emerged as a potential treatment of PNH in pregnancy. This report describes a case of a woman with PNH successfully treated with eculizumab during two pregnancies. Although during both pregnancies she experienced breakthrough hemolysis requiring intermittent blood transfusions, she had no thromboembolic events and had term vaginal births. Granted more research is needed, eculizumab may be an acceptable therapy for PNH in pregnancy.

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1. Introduction

PNH is a rare disease of hematopoietic stem cells caused by acquired mutations in the phosphatidylinositol glycan complementation class A (PIG-A) gene [1]. These PIG-A gene mutations lead to erythrocytes that lack glycosyl phosphatidylinositol (GPI)-anchored membrane proteins like CD55 and CD59, termed PNH erythrocytes [2]. PNH erythrocytes which lack the complement regulatory proteins CD55 and CD59 are more susceptible to complement-mediated intravascular hemolysis than their normal counterparts.

Pregnancy-associated PNH is linked to worse neonatal and maternal morbidity and fetal and maternal mortality rates of 4–9% and 8–12% respectively [3,4]. Hematologically, this includes worsening cytopenia, bleeding, thrombosis, and infection. PNH in pregnancy is associated with higher rates of pregnancy loss, intrauterine fetal demise, small-for-gestational age, premature birth, preeclampsia, eclampsia, hemolysis elevated liver enzymes and low platelet count (HELLP) syndrome, cesarean delivery, increased need for blood product transfusion, and ultimately death [3–7].

Thrombotic events are a serious complication of PNH and account for approximately 50% of all PNH-related deaths [5,6,8]. The risk of thrombosis may be further exacerbated by the hypercoagulable state of pregnancy. There is an even higher risk of complement activation related to tissue injury in the postpartum period [9,10]. Therefore, it is

important to start prophylactic anticoagulant therapy at the confirmation of pregnancy and for it to be continued postpartum [10]. Although allogeneic stem cell transplant is the only cure for PNH, eculizumab has emerged as an alternative treatment option [9].

Eculizumab is a genetically engineered humanized monoclonal IgG antibody targeted at the terminal complement protein C5. Eculizumab binds to C5, blocking its cleavage, and stops the downstream pro-inflammatory cascade and complement mediated cell lysis [9]. Numerous studies have shown that eculizumab is an effective treatment for PNH, leading to stabilization of hemoglobin levels, decreased transfusion requirements, less intravascular hemolysis, and lower rates of thromboembolic events [8,9,11].

Although there are no published studies specifically looking at the use of eculizumab for PNH in pregnancy, there have been numerous case reports showing favorable pregnancy outcomes [4,7]. Danilov et al. 2009 first described initiation of eculizumab in the third trimester of pregnancy for women with PNH [12]. More recently there have been case reports of favorable pregnancy outcomes in women who received eculizumab from conception to delivery [7,13,14]. Herein is described the case of a woman successfully treated with eculizumab for the duration of two pregnancies.

2. Case Presentation

The patient was a 27-year-old Hispanic woman diagnosed one year before her first pregnancy with PNH based on abnormal CD55 and CD59 levels with deficient glycosylphosphatidylinositol-anchored protein (GPI-AP) expression in 38% of granulocytes, 47% of monocytes and

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12% of red blood cells. The patient was counseled about her treatment options for PNH. She elected to continue observation with serial blood tests, given that she was asymptomatic. She received the meningococcal vaccine and started folic acid supplementation.

Nine months later, due to worsening pancytopenia she started eculizumab 600 mg intravenous every 2 weeks. The search for a possible bone marrow transplant (BMT) donor was also started. The patient subsequently had a preconception counseling visit with a maternal-fetal medicine specialist, where the risks of pregnancy with PNH and after BMT were reviewed.

One month after the preconception counseling visit, the patient became pregnant and had prenatal intake at 7 weeks with confirmed pregnancy viability. She began prophylactic enoxaparin subcutaneous daily. Aspirin was withheld as the patient had had no history of arterial thrombosis or other additional cardiovascular risk. A matched, unrelated BMT donor was also found while she was pregnant, but treatment was deferred given that she wanted to continue the pregnancy. The patient experienced breakthrough hemolysis at 9 weeks in her pregnancy, and the frequency of eculizumab was increased to weekly. Blood tests were monitored weekly and transfusion given to keep hemoglobin above 6.5 g/d. Her platelet count decreased to 23,000 without clinical signs of bleeding. She had an early anatomic ultrasound scan which was normal, and limited ultrasound scans every two weeks demonstrated normal fetal growth.

The patient underwent induction of labor at 38 weeks after multidisciplinary coordination with maternal-fetal medicine, hematology and anesthesia. Enoxaparin was held the night before the induction was started. Four units of platelets were given to increase the platelet count before epidural placement. After an uneventful labor induction, the patient underwent a vacuum-assisted vaginal delivery for category 2 fetal heart rate tracing, delivering a viable 3100 g male infant with Apgar scores of 9 at one minute and 9 at 5 min of life. The epidural was removed four hours after delivery after documenting a platelet level of 97,000. No blood transfusions were required intrapartum or postpartum. Enoxaparin was then restarted 12 h after delivery. The patient recovered well and was discharged on postpartum day one with continuation of eculizumab weekly and a six-week course of prophylactic enoxaparin. The patient initially breastfed her newborn but stopped after two weeks due to poor latch and poor milk production. The remainder of her postpartum course was uncomplicated.

Six weeks postpartum eculizumab was changed to every two weeks and enoxaparin was stopped. She followed up with hematology every 3 months and, due to the good control of PNH on eculizumab, BMT was deferred.

Three years later, the patient conceived, and a viable pregnancy was confirmed at 6 weeks of gestation. Her eculizumab regimen was prophylactically changed to weekly and she started prophylactic enoxaparin daily. Blood transfusions were given to maintain hemoglobin at 6.5 g/dL or greater, but her pregnancy was otherwise uncomplicated, with appropriate fetal growth. Labor induction was scheduled at 38 weeks, and eculizumab was then held the week before induction. Enoxaparin was held the night before her induction and the patient was transfused 7 units of platelets to achieve a platelet count of 100,000 for epidural placement. Labor was uneventful, and the patient had a spontaneous vaginal birth of a viable 3090 g male with Apgar scores of 9 at 1 min and 9 at 5 min of life. Two additional units of platelets were given to achieve a platelet count above 100,000 before epidural removal. One unit of packed red blood cells was given for a Hgb of 6.9 g/dL. Enoxaparin was resumed 12 h postpartum and she was discharged on the first postpartum day. Enoxaparin was continued for 6 weeks postpartum.

Ecuzumab dosing was decreased to every 2 weeks at 6 weeks postpartum. After 4 months of exclusive breastfeeding, the patient had a levonorgestrel IUD placed. She has been stable on ecuzumab 600 mg intravenous every two weeks and has not required any blood product transfusions since her last delivery. Growth and development have been unremarkable for both children.

3. Discussion

The patient experienced the most common complications of PNH in pregnancy, which are the increased need for platelet and red blood cell transfusions [4,14]. This can present a diagnostic dilemma as worsening cytopenia can be indicative of progressive PNH, or signs of developing other obstetric complications, including gestational thrombocytopenia, immune thrombocytopenia, preeclampsia or HELLP syndrome.

It is remarkable that both pregnancies were carried to term given that roughly 50% of infants are delivered prematurely in women with PNH [3,4]. PNH can also cause smooth muscle dystonia, which may be associated with protracted labor [9]. Additionally, there is a 30% cesarean delivery rate with PNH³.

Although the role of anticoagulation in women with PNH is controversial, many advocate for starting anticoagulation with the confirmation of pregnancy, especially in the setting of a prior history of thrombotic events [1,9]. Folate and iron supplementation are typically recommended for women with PNH in pregnancy because of ongoing hemolysis, although iron supplementation was withheld in this case because of concerns for iron overload. The patient currently has a levonorgestrel IUD in place, which highlights the importance of a long-acting reversible form of contraception to allow for planned pregnancies in these patients.

Apart from treatment of complement-mediated intravascular hemolysis associated with PNH, clinicians have used ecuzumab to successfully treat atypical hemolytic uremic syndrome (aHUS) [15] and acute kidney injury associated with preeclampsia/HELLP syndrome [16], and it may even be able to prolong pregnancies complicated by early-onset preeclampsia [17]. A review by Stefanovic et al. 2019 highlights the overall improved pregnancy outcomes when ecuzumab is used for these and other conditions. A subgroup analysis in a study by Socie et al. 2019 looking at safety data of ecuzumab over a 10-year period corroborate these findings of improved pregnancy outcomes in women with PNH or aHUS treated with ecuzumab [18].

Although it appears that ecuzumab is safe to use during pregnancy, questions regarding timing of initiation, dosage and frequency, and concurrent use with anticoagulation remain unanswered [7,9,13]. The frequency of ecuzumab was increased to once weekly when breakthrough hemolysis was noted in the first pregnancy in the first trimester, a practice that has also been done by others [4]. Ecuzumab frequency increase was then preemptively done at the confirmation of the second pregnancy to decrease the risk of complications.

Data support that ecuzumab is not associated with anomalies [7,18]. Although initial reports showed no impaired complement function in newborns, a recent report by Duineveld et al. 2019 showed transient complete blockade of the complement system in a newborn of a woman with aHUS treated with ecuzumab [19]. Limited data show that ecuzumab is detectable in cord blood but not detectable in breast milk [4,7,14].

4. Conclusion

In summary, care must be taken when managing PNH in pregnancy given the increased maternal and fetal morbidity and mortality. Providers should anticipate an increased need for blood products due to hemolysis and balance this with anticoagulation requirements to prevent thromboembolic events. Ecuzumab is emerging as a safe treatment option for PNH in pregnancy, although long-term outcomes in infants and children are unknown.

Contributors

Michael J. Fassett cared for the patient and drafted and critically revised the manuscript.

Adrian L. Hernandez Lopez drafted and critically revised the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

Obtained.

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