Successful pregnancy outcome in a woman with Paroxysmal Nocturnal Hemoglobinuria

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare life-threatening disorder caused by an acquired genetic mutation in the hematopoietic stem cells. The mutation results in production of red blood cells with an intrinsic defective in the cell membrane that triggers excessive complement activation.[1] PNH is characterized by complement-mediated hemolysis, thrombosis, and bone marrow failure. PNH primarily affects young adults, including women of childbearing age. Physiological compliment activation that occurs in normal pregnancy can severely exacerbate PNH complications.[2] Woman with PNH have traditionally been counselled against pregnancy due to potential catastrophic maternal and fetal outcomes. Eculizumab is a monoclonal antibody that prevents terminal complement cascade, and has revolutionized the treatment of PNH. However the data on PNH management with Eculizumab during pregnancy is currently limited. We report the first New Zealand case of a successful pregnancy outcome in a patient with PNH treated with Eculizumab.

Case Report

A 35-year-old nulliparous lady with known PNH presented to our Gynaecology Outpatient Clinic in 2017 for pre-conceptual counselling. Pregnancy-associated risks and complications in the context of PNH were discussed. In collaboration with the haematology service, a pre-emptive management plan was created. Her medical history included PNH and heterozygous factor-V Leiden deficiency both diagnosed in 2002. Since then, the patient had sustained multiple thrombotic events and severe anaemia requiring repeat blood transfusions and several episodes of sepsis requiring hospital admissions. Additionally, she was diagnosed with vulval intraepithelial neoplasia in 2017. She had a strong family history of premature menopause. Her medication included Eculizumab started in 2008 for PNH, warfarin anticoagulation and long-term oral penicillin-V antibiotic prophylaxis.

She conceived naturally in 2018 despite of low Anti-Mullerian hormone level during baseline fertility screening. A viable intrauterine pregnancy dating 5-week gestation was confirmed by ultrasound. Warfarin was switched to low molecular weight heparin (Enoxaparin®). She received close follow-up in the antenatal and haematology clinics and fetal progress were closely monitored with serial scans. She remained on Eculizumab and penicillin throughout her pregnancy. The pregnancy was uneventful and fetal assessments were all normal.

An expectant management plan was made for delivery at 37+week gestation. Enoxaparin was withheld for 12 hours prior to elective caesarean section. Caesarean delivery was uncomplicated however she was admitted to ICU post-operatively for close monitoring. Therapeutic Enoxaparin® was reinitiated 12hours postoperatively and Warfarin was started with INR target of >2. On postpartum day 2 she had active bleeding from the caesarean incision wound. A haematoma subsequently developed at the surgical site requiring drainage on postpartum day 11. She was also admitted for mastitis during postpartum week 4 and treated with flucloxacillin.

There were no adverse effects observed in her baby girl. The baby was delivered with good APGAR scores and required no respiratory support. The birth weight was 3.4kg and was in concordance with the pre-delivery estimated fetal growth assessments.

Paroxysmal Nocturnal Hemoglobinuria

In PNH, a mutation in the *PIGA* gene of the X chromosome causes loss of glycosylphosphatidylinositol-anchored membrane proteins, including complement regulators CD55 and CD59. As a consequence, uncontrolled activation of complement on the red blood cell results in accumulation of activated C3 (due to the CD55 deficiency) and subsequently activation of the terminal pathway (due to CD59 deficiency), leading to ongoing intravascular hemolysis (figure 1).[5]

PNH is an uncommon yet life-threatening condition with estimated prevalence of 15.9/1million.[4] PNH manifests with a wide range of symptoms such as fatigue, dysphagia, dyspnoea, abdominal pain and haemoglobinuria. It causes renal dysfunction, pulmonary hypertension, and thromboembolism. PNH is associated with an extremely high maternal risk of thrombosis during pregnancy and postpartum period. It is also associated with higher early pregnancy miscarriage (8%), increased rate of fetal demise (4%) and preterm birth (29%).[3]

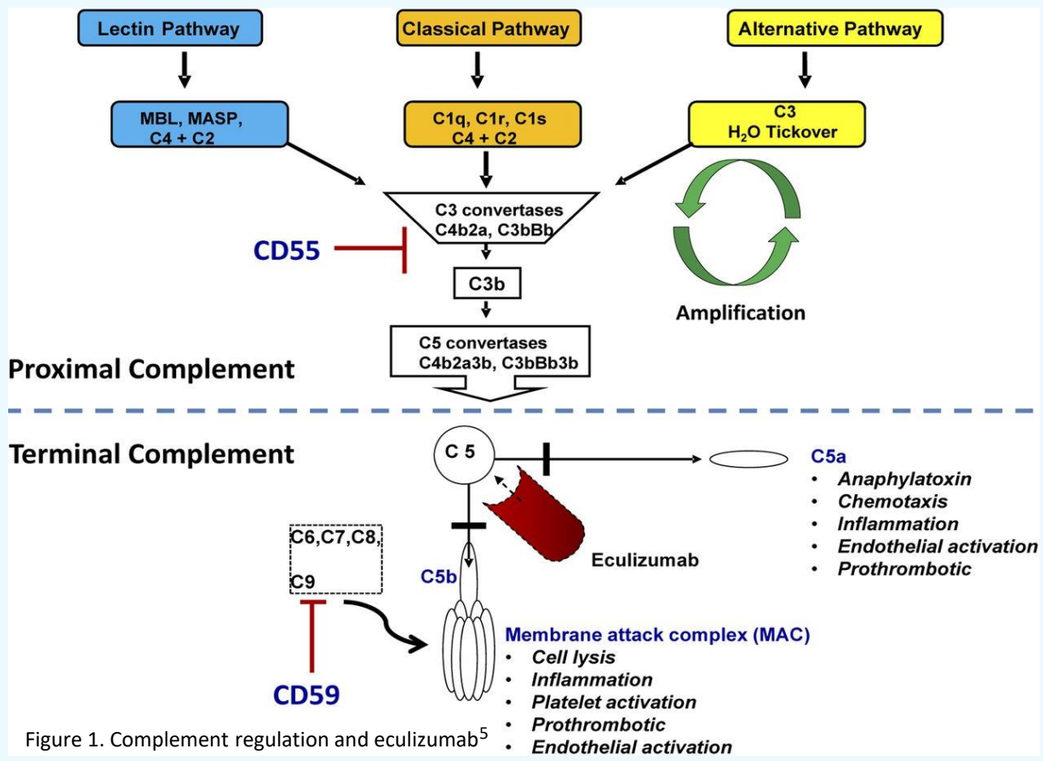

Figure 1. Complement regulation and eculizumab[5]

Eculizumab

Eculizumab is a humanized monoclonal antibody that blocks terminal pathway activation by binding to C5, the first activation protein of this pathway. This prevents formation of the membrane attack complex and C5a, and inhibits complement-mediated haemolysis (figure 1).[5] Eculizumab has been used successfully in the treatment of PNH outside of pregnancy. Case reports regarding the management of PNH with Eculizumab during pregnancy are still emerging in the literature.[1] Eculizumab may provide a safe and effective treatment for PNH during pregnancy. Interestingly, the blockage of the activation of the terminal complement pathway may also be an effective strategy to combat other complement-mediated conditions in pregnancy such as Antiphospholipid syndrome, Sickle cell disease, HELLP syndrome, or in the case of preeclampsia itself.[6] Off-label use of Eculizumab in these complement-mediated conditions has demonstrated clinical improvement, and resolution of hemolysis, thrombocytopenia and liver inflammation along with a prolonged pregnancy.[6] We report this case to contribute our experience of a successful pregnancy outcome in a patient with PNH treated with Eculizumab.

References

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