

## Recurrent thrombotic microangiopathy (TMA) in Pregnancy

Dr Priscilla Smith<sup>1</sup>, Dr Alyaa Abdelmaguid<sup>1</sup>, Ms Katherine Clark<sup>1,2</sup>, Dr Kate Bramham<sup>1,2</sup>  
<sup>1</sup>King's College Hospital, Denmark Hill, United Kingdom, <sup>2</sup>King's College London, , United Kingdom

**Introduction:** Pregnancy induced atypical Haemolytic Uraemic Syndrome (aHUS) is a rare condition affecting 1 out of every 25,000 pregnancies. It is associated with significant long-term morbidity and mortality which may be reduced by prompt diagnosis and treatment. Diagnosis is complicated by similarities in presentation to more common pregnancy complications associated with a thrombotic microangiopathy (TMA) such as pre-eclampsia, new diagnoses of connective tissue disorders and rare but potentially fatal conditions such as thrombotic thrombocytopenic purpura (TTP). Early confirmation of underlying aetiology of TMA is critical to facilitate appropriate management.

**Case:** We report a case of a 22 year old woman with a previous liver transplantation for congenital hepatic fibrosis with recurrent TMA in pregnancy. She presented at 18 weeks in her first pregnancy with generalised swelling, breathlessness and 30kg weight gain. She was found to be hypertensive, proteinuric (urinary Protein: Creatinine Ratio 201.3 mg/mmol) with an acute kidney injury, deranged liver function, thrombocytopenia and evidence of a TMA. TTP was excluded (ADAMTS13 activity 22%) and connective tissue and autoimmune tests were negative. She suffered an intrauterine death in this pregnancy at 22 weeks and a subsequent early miscarriage. Placental histology was unremarkable. Subsequent genetic testing confirmed a complement mutation (heterozygous c.1855G>A (p.Val619Met) variant in exon 15 of the C3 gene), which was not present in the donor liver DNA.

In her next pregnancy she developed a recurrent TMA at 22 weeks' gestation (serum creatinine 199 µmol/l (from baseline 60), platelets 50x10<sup>9</sup>/l and anaemia (Hb 107 g/L). Her blood pressure had increased to 160/100 mmHg, and she had substantial peripheral oedema. Other investigations were unremarkable and fetal scans were reassuring. However, Placental Growth Factor concentration (PLGF) was low <12pg/ml.

In discussion with the National Renal Complement Therapeutics centre treatment with Eculizumab (900mg) was commended but her renal function continued to deteriorate. A second dose (1200mg) was given after 5 days which led to stabilization and improvement in all markers within 3 days. However, fetal demise also occurred on Day 8 of treatment. Placental histology was suggestive of pre-eclampsia.

The patient has subsequently been counselled regarding the uncertainty of her diagnosis and the risk/benefit of prophylactic Eculizumab in a future pregnancy. She is now considering surrogacy for future pregnancies.

**Discussion:** This case highlights the diagnostic uncertainty of pregnancy associated TMA. Low PLGF and placental histology were suggestive of placental insufficiency; however, it remains unknown if these findings were secondary to a TMA triggered by pregnancy in the presence of a complement mutation.

It is important to recognise that the majority of complement proteins are synthesised by the liver, and therefore C3 should have been unaffected in this case due to liver transplantation, but the origin of upregulated complement activity in pregnancy is unknown.

There is increasing use of eculizumab to treat early onset pre-eclampsia, which may present a new therapeutic role for alternative complement pathway inhibitors. However, enhanced understanding of complement activity and its pathogenic role in placental disorders is needed to inform timing and dosing.