10. IS ECULIZUMAB A LIFE-SAVING TREATMENT FOR ATYPICAL HAEMOLYTIC URAEMIC SYNDROME IN LUPUS PREGNANCY?

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Introduction: We report the outcome of an atypical haemolytic uraemic syndrome (aHUS) in a 30 year old British-Asian prima-gravida with Lupus/Sjogren's Syndrome overlap. A combination of therapies including plasma exchange, methylprednisolone pulses and compassionate use of Eculizumab, a c5 inhibiting monoclonal antibody, was lifesaving. The appearance of a microangiopathic haemolytic anaemia (MAHA) and thrombocytopaenia in pregnancy is challenging. The causes can include sepsis, placental abnormalities, anti-phospholipid syndrome, and thrombotic microangiopathies (TMA) including pre-eclampsia/HELLP (haemolysis, elevated liver enzymes, low platelets) syndromes, thrombotic thrombocytopaenic purpura (TTP) and a spectrum of complement mediated conditions thrombotic microangiopathies (also known as atypical haemolytic uraemic syndrome, aHUS). The timings of these complications can vary, presenting anywhere from first trimester to the postpartum period. In a pregnant woman who also has lupus, these presentations can mimic a lupus flare, they are associated with significant maternal and foetal mortality; even with survival there can be life-changing sequelae. Eculizumab is a recombinant humanized monoclonal antibody which acts as a terminal inhibitor of the complement cascade and was approved for use in aHUS in the UK in 2015: use in lupus is rare and illustrates important learning points.

Case description: A 30 year old British-Asian woman had a diagnosis of with lupus/Sjogren's syndrome overlap and non-progressive interstitial lung disease. Her autoantibody profile included positivity for anti-Ro and anti-La antibodies and for rheumatoid factor. Complement C3 and C4 levels and quantitative double stranded DNA remained in physiological range and she had persistent low level haematuria and proteinuria with preserved renal function. She was maintained on 200 mg of hydroxychloroquine and up to 20 mg of prednisolone daily, having failed a trial of methotrexate. Other disease modifying anti-rheumatic drugs such as azathioprine were considered but this choice was complicated by low thiopurine methyltransferase level, and the patient declined. She had one episode of post-anti-streptolysin O positive arthralgia and renal impairment which settled with an increased steroid course. Three years after initial diagnosis she was able to conceive naturally. In early pregnancy, her condition was reported as stable, and she was referred to a combined rheumatology/obstetrics clinic. In the nineteenth week of pregnancy, she presented to the emergency department with multi organ involvement including acute confusion, multiple epileptic seizures, acute renal and cardiac insufficiency, and absence of foetal heartbeat. Haematology investigations showed thrombocytopaenia, reduced haptoglobins, and the presence of schistocytes on blood film in keeping with a microangiopathic haemolytic anaemia (MAHA). There was nephrotic range proteinuria (2300 mg/mmol) and creatinine had doubled from previous baseline to 109 micromol/L. Her condition became critical and she was transferred with life threatening thrombotic microangiopathy to the local tertiary centre for access to plasma exchange. She required intensive care admission with invasive ventilator support and a tracheostomy. Magnetic Resonance Imaging of her brain was consistent with posterior reversible encephalopathy syndrome (PRES). An echocardiogram showed moderate left ventricular systolic dysfunction with regional wall motion abnormalities. At nineteen gestational weeks, the presence of MAHA, thrombocytopaenia and acute renal injury was compatible with several possible overlapping diagnoses. This included sepsis with disseminated intravascular coagulation (DIC), anti-phospholipid syndrome,

pre-eclampsia/HELLP and thrombotic microangiopathies including thrombotic thrombocytopaenic purpura (TTP), and haemolytic uraemic syndrome (HUS). She had normal prothrombin and activated partial prothrombin times thus making DIC less likely. There was no evidence for antiphospholipid syndrome. She did not fulfil the criteria for HELLP with normal liver function tests. TTP was considered less likely with normal value for ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) although it is known that TTP in lupus may be associated with normal ADAMTS13 activity. A diagnosis of aHUS was proposed. This is controversial in the presence of lupus with some definitions treating lupus itself as an exclusion criterion in aHUS. In 50% of aHUS cases, genetic testing shows abnormalities within the complement cascade including mutations in complement factors I and H, and complement regulatory genes but these results are rarely available when therapeutic decisions are being made. An aHUS gene panel was requested but was later reported as negative. Despite these considerations, a diagnosis of sporadic atypical HUS was consistent with the presenting features and this diagnosis was supported by renal biopsy carried out during the recovery phase which showed features consistent with eclampsia and aHUS. Our patient was initially managed with a therapeutic evacuation of the uterus. She was commenced on a regime of plasma exchange and 3 pulses of 500 mg of methylprednisolone with no clinical improvement. Due to the grave outlook, an application for compassionate use of Eculizumab, a c5 inhibiting monoclonal antibody was made to the National aHUS Service in Newcastle. She received 2 infusions of Eculizumab and best supportive care and made a full cardiac, haematologic and neurologic recovery. In cases of chronic aHUS with a confirmed genetic cause, lifelong treatment with Eculizumab can be considered. Given the full recovery made by this patient and the absence of a demonstrable mutation, there was no rationale for continuing Eculizumab. Following recovery, the patient's condition has been further complicated by a recurrence of PRES one year after these events. Further brain imaging showed white matter lesions of uncertain age and she now remains on anti-epileptic medications, low dose prednisolone and azathioprine. The patient has now discontinued Azathioprine and wants to try and get pregnant again.

Discussion: Mild complications are common in lupus pregnancies, and the risk of foetal loss is 2-3 times higher than in the normal population; maternal life-threatening complications are less common but can be devastating. Thrombotic microangiopathy (TMA) in pregnancy can be classified into several (overlapping) clinical variants. One of these is atypical HUS which represents 10-15% of the total incidence of TMA and is associated with significant mortality. In atypical HUS, there is continuous activation of the alternative pathway of the complement cascade culminating in the production of C5a. Atypical HUS can be triggered by infections (the most common being Streptococcus pneumoniae), systemic conditions (including lupus), pregnancy and drug therapies. In atypical HUS associated with pregnancy and the post-partum period, 50% of cases are associated with known mutations in complement regulation pathways. By inhibiting C5 conversion to C5a, and reducing activity of the alternative complement pathway, Eculizumab, the second most expensive drug currently available worldwide, has revolutionised care for patients with aHUS. The current indications for lifelong Eculizumab treatment include paroxysmal nocturnal haemaglobinuria and some cases of atypical HUS. It is rarely used in the absence of proven genetic causes or when there is a concurrent lupus diagnosis, which makes its use in this case noteworthy. Do you agree that this is a case of aHUS in a lupus pregnancy? Is further pregnancy absolutely contraindicated? Should Eculizumab have a role in the management of atypical HUS in the absence of known mutations of the complement pathway? What other immunosuppressive therapy might be considered in the ongoing management of this patient? Was the previous Streptococcal infection (with positive ASOT test) relevant for development of HUS in pregnancy? What is the relevance of recurrent PRES in this patient and is there a link between PRES and the TMA spectrum of disease?

Key learning points: Challenges of timely diagnosis and management of thrombotic microangiopathies in lupus pregnancy Use of Eculizumab in cases of atypical haemolytic uraemic syndrome