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Journal
Rheumatology, 57(suppl_5)

ISSN
1462-0324

Authors
Edens, Cuoghi
Rodrigues, Bruna Costa
Lacerda, Marcela Ignacchiti
et al.

Publication Date
2018-07-01

DOI
10.1093/rheumatology/key172

Peer reviewed

RHEUMATOLOGY

Rheumatology 2018;57:v18–v25
doi:10.1093/rheumatology/key172

Challenging cases in rheumatic pregnancies

Cuoghi Edens[1,2], Bruna Costa Rodrigues[3,4], Marcela Ignacchiti Lacerda[3,4], Flavia Cunha Dos Santos[3,4], Guilherme R. De Jesús[3,4], Nilson Ramires De Jesús[3,4], Roger A. Levy[3,4], Cianna Leatherwood[5], Jess Mandel[6] and Bonnie Bermas[7]

Abstract

This article describes three complicated cases in rheumatology and pregnancy. The first case elucidates the challenges in treating SLE in conjunction with pulmonary arterial hypertension, while the second case features an SLE-affected pregnancy with development of portal hypertension secondary to portal vein thrombosis related to APS. The third case is a pregnant woman with stable SLE who developed thrombotic microangiopathy caused by atypical haemolytic uraemic syndrome, and failed to improve despite multiple measures including biopsy and elective preterm delivery. There are grave and unique challenges for women with autoimmune disease, but adverse outcomes can sometimes be avoided with careful and multidisciplinary medical management. Pre-conception counselling with regard to medications and disease treatment should also include discussion of the advisability of pregnancy, which may be difficult for a patient, but present the best course for optimizing health outcomes.

Key words: anti-phospholipid syndrome, portal vein thrombosis, portal hypertension, pregnancy, pulmonary arterial hypertension, scleroderma, stillbirth, systemic lupus erythematosus

Rheumatology key messages

- Rheumatic diseases in pregnancy present with a wide range of symptoms and present significant clinical challenges.
- Cases presented demonstrate that keeping a broad differential diagnosis is essential to providing the best care.

REVIEW

Introduction

Women with rheumatic disease can present with a myriad of symptoms, some causing catastrophic illness. The three cases presented here demonstrate that pregnancy can be complicated by a wide range of ailments and that keeping an open mind and a wide differential diagnosis can be essential to providing the best care. Each patient described has a serious underlying rheumatic disease that, taken alone, can often be successfully managed in pregnancy with careful planning, strong medications and close attention. But each woman described developed an unexpected and rare complication that put her life—and the life of her unborn child—in peril.

[1]Division of Pediatric Infectious Diseases and Rheumatology, Rainbow Babies and Children's Hospital, [2]Division of Rheumatology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA, [3]Department of Obstetrics, [4]Department of Rheumatology, Hospital University Pedro Ernesto – Universidade do Estado do Rio de Janeiro, Rio de Janiero, Brazil, [5]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [6]Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego School of Medicine, San Diego, CA and [7]Division of Rheumatic Diseases, University of Texas Southwestern, Dallas, TX, USA

Submitted 31 October 2017; revised version accepted 11 May 2018

Correspondence to: Edens Cuoghi, Division of Pediatric Infectious Diseases and Rheumatology, Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, Cleveland, OH 44106, USA.
E-mail: cuoghi.edens@gmail.com

Case 1

The patient is a 24-year-old African American female diagnosed with SLE at age 18 years after presenting with arthritis, malar rash, leucocytoclastic vasculitis, fevers, fatigue, anaemia and lymphopenia. At diagnosis she had a high titre ANA and positive Smith, RNP, SmRNP and aPL. At age 21 years she was diagnosed with WHO class IV/V LN causing chronic proteinuria of 2 g/l and had been prescribed mycophenolate. After an unplanned pregnancy resulting in miscarriage while on mycophenolate at age 22 years, this medication was stopped and she was started on tacrolimus and AZA. Her medications at presentation included AZA, HCQ, prednisone 15 mg/day, aspirin, lisinopril and tacrolimus.

Table 1 Objective parameters of PAH in a pregnant patient while on epoprostenol

Gestational age	20 weeks 4 days	23 weeks 3 days	27 weeks 6 days
Epoprostenol dose	None	6 ng/kg/min	12 ng/kg/min
6MWT predicted distance (m)	477	478	470
6MWT actual distance (m)	332	375	424
6MWT distance predicted (%)	70	78	90
Borg score[a]	3	2	2
BMI (kg/m^2)	40.9	40.7	41.8

[a]Borg Rating of Perceived Exertion Scale, 0 = none 10 = maximum. PAH: pulmonary arterial hypertension; 6MWT: 6 min walk test.

At a routine rheumatology appointment, she reported a dry cough and dyspnoea on exertion. A chest radiograph revealed perihilar congestion and cardiomegaly. Her echocardiogram was notable for a preserved ejection fraction, an enlarged right ventricle (RV) with reduced contractility, moderate tricuspid regurgitation and a small pericardial effusion. Out of concern for pulmonary hypertension, right heart catheterization (RHC) was scheduled. Per protocol, a pre-procedure urine pregnancy test was collected and returned positive. The procedure was cancelled. The cardiologist started furosemide, discontinued her lisinopril and she was continued on the rest of her outpatient medication regimen.

Three months later, at 20 weeks gestation, she was seen in the pulmonary hypertension clinic at a different medical facility with dyspnoea on exertion, rapid weight gain, peripheral oedema, hypertension (149/94 mmHg) and a BMI of 41. Cardiac auscultation found a split S2, accentuated P2 and 1/6 systolic murmur at the left lower sternal border. She had 1$^+$ pitting pretibial oedema, trace oedema in the hands and periorbital oedema. Her labs were notable for mild anaemia, low albumin (1.4 g/dl), hypocomplementaemia and 2.5 g/l proteinuria with normal creatinine, platelets and liver enzymes. Consistent with her prior history, she had a high titre ANA and positive Smith, Sm/RNP and RNP antibodies, however, she also had a low-positive dsDNA titre and her aPL testing was negative.

She was admitted to the hospital from the clinic for further workup. Her echocardiogram had a preserved ejection fraction but volume overload, a moderately enlarged RV and RA, and a small pericardial effusion. The RV systolic pressure was 63 mmHg. Echocardiogram findings were concerning for moderate pulmonary hypertension. A ventilation–perfusion scan was read as low probability. RHC was performed and demonstrated a pulmonary arterial pressure of 42 mmHg, consistent with moderate pulmonary arterial hypertension (PAH), presumably type 1, secondary to her SLE. Epoprostenol was initiated at 2 ng/kg/min, with near resolution of her peripheral oedema and dyspnoea. Lengthy discussions were had with the patient, her medical teams and her family due to the mortality risk that PAH conveys to both mother and foetus as well as the theoretical threat of pre-term labour with epoprostenol therapy. She desired to continue the pregnancy. Enoxaparin was started due to the likelihood of thrombosis secondary to SLE, gravid state, PAH, obesity, proteinuria, indwelling central line and prostacyclin use. Discharge medications included higher-dose furosemide, metoprolol, continuous epoprostenol and an increased dose of tacrolimus, in addition to her prior SLE medications. Epoprostenol was titrated to 12 ng/kg/min after discharge, with subjective and objective improvement, illustrated in Table 1.

At her 33 week prenatal visit, she described worsening dyspnoea and the inability to lay supine. On examination, she had 3$^+$ pitting oedema to the thigh, edematous hands and a blood pressure of 147/99 mmHg. She had gained 15 pounds since her recent appointment. Her brain natriuretic peptide, platelets, liver enzymes and creatinine were normal, however, her urine total protein was very elevated at 16 g/l and complements were lower than at her PAH diagnosis (Table 2). Urinalysis returned with 15 white blood cells (WBCs)/high-power field (hpf), 5 red blood cells (RBCs)/hpf, hyaline and cellular and granular casts. The tacrolimus level was low. An echocardiogram showed a hyperdynamic left ventricle, severely dilated RV and RA and a moderate pericardial effusion. All SLE medications were continued, tacrolimus increased and diuresis was attempted. She remained on epoprostenol 12 ng/kg/min. She was given betamethasone for foetal lung maturation. Increasing doses of metoprolol and methyldopa were trialled due to worsening hypertension. Out of concern for SLE flare manifesting as worsening proteinuria, hypocomplementaemia and pericardial effusion, prednisone was increased from 15 to 60 mg/day. Three days after this increase, she began having headaches and blurred vision with systolic blood pressures $>$180 mmHg. Magnesium infusion was begun with concern for superimposed preeclampsia, although uric acid, liver enzymes and platelet count did not suggest this aetiology.

Due to her worsening clinical picture as well as new foetal heart rate decelerations, an urgent caesarean delivery under general anaesthesia was performed at 33 weeks 4 days gestation. She received intraoperative stress-dose steroids. Cardiothoracic surgery, cardiac and obstetric anaesthesia and the extracorporeal membrane oxygenation team, as well as obstetrics, neonatology and pulmonary specialists were present for her uncomplicated delivery and bilateral tubal ligation. A healthy boy, Apgar scores 8/9, was delivered. After delivery she was admitted to the surgical intensive care unit (ICU) and her course was complicated by a large postpartum haemorrhage. While his mother was recovering,

Table 2 Laboratory value at initial PAH visit and subsequent worsening 13 weeks later

Lab	20 weeks gestation	33 weeks gestation
WBC count ($\times 10^9$/l)	5.4	4.8
Haemoglobin (g/dl)	10.5 low	9.8 low
Platelets ($\times 10^9$/l)	260	369
Creatinine (mg/dl)	0.42	0.50
Albumin (g/dl)	1.6 low	1.4 low
AST (U/l)	18	18
ALT (U/l)	14	15
C3 (mg/dl)	57	48 low
C4 (mg/dl)	12 low	11 low
Anti-dsDNA (IU/ml)	10.0 positive	6.0 positive
Spot urine protein (g/l)	4.0 high	16.5 high

ALT: alanine transaminase; AST: aspartate transaminase.

the newborn spent 1 week in the neonatal ICU receiving routine care and had no significant events or interventions. The patient was continued on her prior outpatient medication regimen, including epoprostenol with a prednisone taper, and demonstrated no evidence of post-partum SLE flare. Both were discharged from the hospital at 1 week post-partum, at which time her spot urine total protein was 4.5 g/l.

Discussion

This case presents many challenging clinical dilemmas. In general, those with SLE can and do have successful pregnancies. Patients should be counselled, however, that improved outcomes for both mother and baby occur when pregnancies are planned, allowing for the cessation of teratogenic medications and disease control, making reproductive health counselling an essential part of their rheumatologic care. Initially our patient was denied an RHC due to her gravid state, however, this is not a contraindication for this procedure [1]. As an RHC does not use contrast or fluoroscopy, risks for the foetus are low when compared with left heart catheterization. RHC complications include bleeding or bruising, pneumothorax and more rarely air embolism, arrhythmia, thrombosis, infection, tamponade and pulmonary artery rupture, but there are no reports of these being more frequent in pregnancy; in fact, pulmonary artery catheters are common in obstetric intensive care. Echocardiography in pregnancy actually overestimates pulmonary pressures, potentially leading to too-frequent diagnosis of PAH, highlighting the need for RHC in obstetric patients [2, 3].

While pregnancy and the diagnosis of PAH occurred concurrently in this case, PAH itself is an indication to advise against conception in those with or without CTD [4]. The European societies for cardiology and respiratory diseases have limited guidelines about PAH and pregnancy, but these include that pregnancy should be discouraged and contraception, including medical sterilization, is indicated; termination should be discussed if a woman is pregnant; and 'disease-targeted therapies, planned elective delivery and effective close collaboration between obstetricians and the PAH team' are important [5]. Patients with PAH should be offered medical sterilization and reliable contraception modalities. Based on the greatly increased risk for morbidity and mortality, termination of pregnancy should be offered independent of functional status or objective findings. This recommendation is based on the known increased risk of morbidity and mortality.

Studies prior to prostaglandin therapy estimate a 50% chance of mortality to both mother and baby [6]. More recent studies estimate the probability of death to be 18–40% [7–11], and it is higher in women with rheumatologic disorders, often due to complications from pre-eclampsia and disease flare. A majority of these deaths are attributed to RV failure, although they are often multifactorial, involving respiratory failure, kidney failure and haemorrhage. International case studies reporting PAH and prostacyclin administration in pregnancy have demonstrated that starting this medication early in pregnancy leads to an improved survival rate [10, 12–18], although pre-term delivery is still present in >50% of cases. It does not appear from these case studies that prostacyclin therapy has a teratogenic effect. The preferred prostacyclin delivery is parental. This mode of delivery is the most efficacious, has a rapid onset of action, titrates easily and has been successfully paired with oral phosphodiesterase 5 inhibitors sildenafil and tadalafil. Both epoprostenol and treprostinil are classified as pregnancy category B, ilioprost is category C. Inhaled prostacyclins have been used but are recommended for mild classes of heart failure without significant RV changes. Calcium channel blockers have also been used with success and are safe in pregnancy. On the other hand, endothelin receptor antagonists and soluble guanylate cyclase stimulator are not recommended in pregnancy due to teratogenicity concerns.

Regarding delivery mode, there is no expert consensus whether caesarean or vaginal delivery is safest for women with PAH [5, 19, 22]. Theoretically vaginal deliveries have more haemodynamic complications due to Valsalva manoeuvres and associated natural neurologic sequela of childbirth. Anaesthesia for caesarean delivery must be chosen carefully as there are also inherent haemodynamic risks with general anaesthesia. PA catheterization may be useful in either mode of delivery, but is not standard. No matter the mode, delivery should be planned and performed at a centre with a multidisciplinary team able to care for both mother and baby. Of note, the highest incidence of thrombosis, cardiac decompensation and death in reported cases of PAH is within the first week post-partum. Patients should remain hospitalized during this period and anticoagulation considered [19]. Anticoagulation is controversial in PAH, even independent of the pregnant state, due to side effects, particularly bleeding, as was seen in this patient [4]. All patients should be closely followed post-partum, as they are still at risk for haemodynamic compromise.

Table 3 Serum complement reference ranges in healthy pregnant females

Complement	Non-pregnant adult	First trimester	Second trimester	Third trimester
C3	83–177	44–116	58–118	60–126
C4	16–47	9–45	10–42	17–37

Information summarized from Gronowski [20]. All units are milligram per decilitre.

It is difficult to determine whether this patient had pre-eclampsia or if her clinical worsening was an evolution of her lupus. Arguing for pre-eclampsia was her gestational age, rising blood pressure, headaches, dramatic increase in proteinuria, the absence of other lupus symptoms, as well as her rapid improvement following delivery. Arguing against pre-eclampsia was that her platelets, hepatic function and uric acid were all normal, her tacrolimus level was low, putting her at risk for renal disease flare, and she had declining complement levels. Complicating the latter aetiology, C3 and C4 can be low during pregnancy even without a diagnosis of SLE [20] (Table 3). Out of concern for a lupus flare, she received an increased prednisone dose, which has a known side effect of hypertension, which possibly led to her headaches and vision changes and confounded her case. Aetiological consideration was also given to cardiac tamponade or worsening pulmonary hypertension. Her moderate pericardial effusion improved quickly with concurrent diuresis and prednisone, ruling out tamponade, but without further elucidation of the causation of her decompensation. While she did not undergo an RHC or have a pulmonary artery catheter placed, she improved without titration of her epoprostenol, making worsening PAH unlikely. PAH affects the ability to increase cardiac output and increases pulmonary vascular resistance. These altered haemodynamics, accompanied by the cardiovascular effects of pregnancy and the theoretical pathophysiology of pre-eclampsia involving increased plasma volume and reduced systemic vascular resistance due to the uterine spiral artery failure, may explain the decompensation seen in this patient and others with PAH.

This case is an example of a successful, unplanned pregnancy and concurrently diagnosed PAH in a patient with well-controlled SLE with baseline proteinuria. This patient's course emphasizes the importance of recognizing PAH and pursuing a full evaluation as well as beginning treatment early in pregnancy for improved outcomes. Parenteral prostanoids have been shown to be safe and advantageous in pregnancy, as seen in this case. Without this treatment, mortality rates are unacceptably high, but with therapy the risks may be modified, although data do not exist to demonstrate the extent of the improvement. This case also highlights the challenges of determining whether a patient has pre-eclampsia or a lupus flare—patients with SLE being at risk for both.

Case 2

A 29-year-old Brazilian Afro-descendant patient, born and living in Rio de Janeiro, was admitted to our high-risk pregnancy clinic for women with systemic autoimmune diseases at the Hospital Universitário Pedro Ernesto in Rio de Janeiro, Brazil, in January 2016. It was her fifth pregnancy; she reported having one healthy 11-year-old son, one previous neonatal death due to congenital heart disease and two stillbirths at 29 and 32 weeks of gestation, respectively, with the last delivery complicated by pre-eclampsia and placental abruption. The patient was first examined at our clinic at 23 weeks of gestation presenting with ascites, recent upper gastrointestinal bleeding and haemodynamic instability (syncope and dyspnoea). She was admitted to the hospital and managed with clinical support, blood transfusion, removal of 2 l of ascitic fluid by paracentesis and endoscopic ligation of oesophageal varices for extra-hepatic portal vein obstruction (EHPVO). She reported presenting the same signs and symptoms during the previous two pregnancies that resulted in stillbirths. At that time her physicians treated the oesophageal varices with endoscopic sclerotherapy, but no further investigation was performed. The patient had a history of alcohol use from ages 20 to 24 years, but denied present consumption of alcohol. The laboratory workup revealed high titre aCL (145 G phospholipids and 129 M phospholipids), that were persistent, with negative anti-beta 2 glycoprotein I, LA and ANA tests. A complete blood cell count showed anaemia and thrombocytopenia (haemoglobin 6.8 mg/dl, platelet count 82 000 cells/mm^3); serologic tests for syphilis; hepatitis viruses A, B and C and HIV were negative. The cultures of the ascitic fluid were negative and cytology showed the absence of neoplastic cells. Abdominal Doppler US identified partial recanalization of an old portal vein thrombosis (cavernomatous transformation of the portal vein), homogeneous splenomegaly, voluminous ascites and no signs of chronic liver disease. An upper gastrointestinal endoscopy showed thin and intermediate thickness oesophageal varices and mild portal hypertensive gastropathy. The final diagnosis was portal hypertension secondary to portal vein thrombosis related to APS type 2 [21] with thrombotic and obstetric events as classical manifestations and thrombocytopenia as a non-criteria manifestation [22–24].

After 13 days of hospitalization and no further bleeding event, the patient was discharged in stable condition, with prescriptions for enoxaparin 40 mg/day, diuretics (furosemide and spironolactone), a β-blocker (propranolol) and an iron supplement. She was followed for prenatal care at our centre and remained stable until term, undergoing labour induction at 39 weeks of pregnancy, with a live-born baby girl of 2800 g. The Apgar scores were 9 at the 1 and 5 min following an uncomplicated vaginal delivery. There was no need for ICU admission for the mother or the infant. Both were discharged 48 h after delivery with routine observation. She was asymptomatic at the follow-up visits at 20 and 48 days after delivery. The use of s.c. enoxaparin was kept at 40 mg/day for 6 weeks post-partum, as well as the remainder of the

medications for portal hypertension treatment. The patient was referred back to the gastroenterology and rheumatology clinics for ongoing follow-up.

We decided not to add low-dose aspirin to enoxaparin due to the high bleeding risk in this patient. Twenty-one pregnancies in 12 patients with EHPVO were studied in a single centre in New Delhi, India [25]. The authors called attention to the fact that the increase in blood volume and cardiac output related to pregnancy overloads the portal flow, aggravating pre-existing portal hypertension and increasing the risk of variceal bleeding during pregnancy. It has been previously demonstrated that pregnancy is safe in women that have undergone endoscopic sclerotherapy or endoscopic ligation of oesophageal varices [26]. In the study mentioned above [25], there was no significant difference between those that had variceal ligation or endoscopic sclerotherapy in terms of pregnancy outcome and complications. There were no stillbirths or maternal mortality. The authors concluded that pregnant EHPVO patients should be managed in a tertiary care centre with a multidisciplinary approach. In the case reported here, we determined the cause of EHPVO and managed the patient according to the recommendations of Subbaiah *et al*. [25], in addition to treating the patient for APS-related obstetric complications.

Case 3

A 27-year-old G2P1 Hispanic woman with a history of SLE presented to the hospital at 25 weeks 6 days gestation with a 1 week history of worsening shortness of breath, productive cough, fatigue and rhinorrhoea. The patient was diagnosed with SLE at age 17 years when she presented with discoid lesions, arthritis, mononeuritis multiplex, RP in the setting of a positive ANA titre and dsDNA. At age 21 years she developed biopsy-proven class II and V LN and was treated with high-dose steroids, MMF and enalapril. Her serologies are notable for an ANA of 1:2560; positive Ro, RNP, Smith and dsDNA antibodies; hypocomplementaemia and negative aPL panel. Her past medical history is remarkable for primary biliary cirrhosis treated with ursodiol. Previous treatments include AZA (complicated by pancreatitis), MMF (discontinued due to insurance), CYC (complicated by severe cytopenia), rituximab (ineffective), tacrolimus (ineffective) and belimumab. Her prior obstetrical history is significant for one previous planned pregnancy in 2013. Six months prior to her first pregnancy the patient transitioned from MMF to ciclosporin. The pregnancy was complicated by anaemia, pleuritis, increased blood pressure, 8 g/day of proteinuria and worsening skin rashes. Treatment during pregnancy included prednisone of 30 mg/day and several IVIG infusions, in addition to the aforementioned medications. The patient was delivered by caesarean section at 36 weeks for breech position and premature rupture of the membranes. The post-partum period was complicated by hypertension.

Following the first pregnancy, the patient had the placement of an intrauterine device (IUD) and resumed MMF at 3 g/day. After missing one cycle of her menses, the patient was found to be pregnant by a urine pregnancy test. Vaginal US revealed that the IUD had been dispelled and the presence of an intrauterine gestational sac of 7 weeks 4 days. Active medications included ciclosporin 100 mg by mouth twice a day, HCQ 200 mg/day by mouth, calcium and vitamin D, ursodiol 300 mg by mouth three times a day, labetalol 400 mg by mouth twice a day, levothyroxine 150 μg/day by mouth, aspirin 81 mg/day by mouth and prednisone 20 mg/day by mouth. At the time of her pregnancy diagnosis her skin disease was active and her urine protein:creatinine ratio was 7.48 with a serum albumin of 2.0 g/l, C3 was 65 mg/dl and C4 was 15 mg/dl. She was counselled on both the high-risk nature of the pregnancy and the potential risks to the foetus associated with MMF exposure: the patient elected to continue the pregnancy. MMF was discontinued and ciclosporin was initiated and increased to a dose of 125 mg twice a day (selection of ciclosporin was based on its successful use during her first pregnancy). Her prednisone dose was increased to 20 mg/day and labetalol and furosemide were added.

At week 22 of gestation she presented as an outpatient with worsening shortness of breath and was diagnosed with fluid overload. Her furosemide dose was increased to 80 mg/day. Three weeks later at gestational age 25 weeks 6 days, she presented with a 1 week history of worsening shortness of breath, productive cough, fatigue and rhinorrhoea. Her creatinine was 0.88 mg/dl, 24 h urine protein was 1.6 g, C3 was 102 mg/dl and C4 was 18 mg/dl. Her urinalysis showed no casts, 0 RBCs/hpf and 5–10 WBCs/hpf. Her chest radiograph showed a left lower lobe consolidation consistent with pneumonia and the sputum culture grew methicillin-sensitive *Staphylococcus aureus*. The patient had been on prednisone of 10–20 mg for weeks and therefore infection was one of the greatest concerns. As therapy with vancomycin and ceftriaxone was initiated, prednisone was switched to methylprednisolone 16 mg/day i.v. to ensure appropriate systemic absorption and her ciclosporin was discontinued. Despite this therapy, she developed acute respiratory distress syndrome requiring intubation and subsequently became oliguric and required renal replacement therapy. Attempts at extubation were complicated by tachycardia and tachypnea. In an effort to improve her respiratory status, at 26 weeks 6 days the patient underwent an emergency caesarean section with delivery of a boy with Apgar scores of 2 and 4 and a weight of 670 g. Shortly after her caesarean section, her labs were notable for decreased complements (C3, 46 mg/dl; C4, 10 mg/dl), dsDNA of 22 IU/ml, 24 h urinary protein of 2.2 g, haemoglobin of 6.8 g/dl with 1+ schistocytes on a smear, platelets of $136 \times 10^3/\mu l$ and urinalysis with granular casts. A renal biopsy was performed 3 days after delivery to elucidate the nature of her renal failure and demonstrated thrombotic microangiopathy (TMA), stable class V LN, with superimposed acute tubular necrosis. Workup of the TMA revealed negative aPL and negative ADAMTS13 and the presumptive diagnosis of atypical haemolytic uraemic syndrome (aHUS) was made. Therapy with plasmapheresis and eculizumab was initiated and with this

combination she was able to be extubated and weaned off of supplemental oxygen. Her renal function improved during the subsequent 2 weeks and she no longer required renal replacement therapy. She was pending discharge to a rehabilitation facility when she developed an irreversible coagulopathy of unknown aetiology and died. Autopsy was not performed as per family wishes.

Discussion

The differential diagnosis of acute renal failure in this pregnant SLE patient includes LN, pre-eclampsia, acute tubular necrosis, hypertensive emergency and thrombotic microangiopathies. While renal biopsy has an increased rate of complication during pregnancy, it is not contraindicated [27]. LN was a distinct possibility given her prior history of class V LN. Tedeschi *et al.* [28] showed that in SLE, a patient's flare during pregnancy is likely to follow the same organ pattern as disease activity within 6 months of pregnancy. However, this patient's low dsDNA level and normal complements at the start of her clinical presentation with minimally active urine sediment made LN flare less likely. Pre-eclampsia, manifesting with hypertension and proteinuria, is a complication reported in >20% of SLE pregnancies [29]. Patients with LN and/or APS are at an even higher risk of pre-eclampsia during pregnancy, and this patient was on low-dose aspirin as recommended by the EULAR [30] for prevention of pre-eclampsia or pre-term labour. The official recommendations support initiation of low-dose aspirin prior to conception or before 16 weeks gestation, and this patient was placed on it after learning of the pregnancy at 7 weeks gestation. While this patient certainly was at risk for pre-eclampsia, during much of her hospitalization she was hypotensive due to sepsis. This patient was a risk for thrombosis with her ongoing proteinuria but was not anticoagulated. Thus the renal biopsy was crucial in identifying and appropriately treating the active pathology in this patient. The predominant biopsy finding in this patient was TMA without glomerular endotheliosis.

TMA is a clinical syndrome associated with thrombocytopenia, microangiopathic haemolytic anaemia and renal failure with a characteristic appearance on biopsy specimen [31]. Our patient possessed all of these features. Thrombotic thrombocytopenia purpura, a more common cause of acquired primary TMA, was ruled out in this patient with a normal ADAMTS13 level. TMA can be seen in cases of pre-eclampsia, but it is more commonly associated with glomerular endotheliosis in which the glomeruli appear enlarged and hardened due to the inability of blood to pass through the narrowed capillaries [32]. The HUSs are a class of conditions also associated with TMA and should be considered in a case of TMA associated with hypocomplementaemia. These include typical HUS (Shiga toxin mediated), aHUS, secondary HUS and idiopathic HUS [33]. Causes of secondary HUS include pregnancy; haemolysis, elevated liver enzymes and low platelet count syndrome; drug associated; sepsis; disseminated intravascular coagulation; autoimmune disorders including SLE; APS; malignancy and streptococcal infections [34]. Her stable SLE clinical manifestations suggested that SLE was not the primary driver of her HUS. Her sepsis had responded to antibiotics, making this too an unlikely cause of secondary HUS, and the patient lacked aPL on several occasions, ruling out APS. The findings of TMA on renal biopsy in the setting of low complement levels with improved sepsis, no evidence of active SLE and negative ADAMTS13 were consistent with aHUS.

aHUS is a disorder in the complement alternative pathway system and is responsible for an estimated 10% of HUS in adults [35]. First-line treatment is plasmapheresis, but the evidence for the success of plasmapheresis in aHUS is not as robust as the evidence for treatment in thrombotic thrombocytopenic purpura [36]. Plasmapheresis was initiated in this patient, however, after 3 days she had not improved and discussions were initiated regarding anti-complement therapy with eculizumab. Eculizumab is a mAb to C5 and a terminal complement inhibitor, preventing formation of the membrane attack complex (C5b-C9) and thus halting the cytokine activation and pro-inflammatory effects of complement consumption [36]. This medication is an approved treatment for paroxysmal nocturnal haemoglobinuria and aHUS. While there are no randomized clinical trials to evaluate the use and safety of eculizumab in pregnancy, case reports for aHUS [37] and case series and a review of paroxysmal nocturnal haemoglobinuria [38–40] suggest no increased risk in complications with the medication during pregnancy. The decision to proceed with this treatment after the diagnosis was made following delivery was driven by her critical clinical status and absence of alternative therapies. With eculizumab therapy her haemolytic anaemia and renal insufficiency reversed, suggesting that complement activation was driving her renal disease.

Conclusion

The differential diagnosis for a patient with SLE and renal failure is broad, particularly in the setting of sepsis. Pregnancy, autoimmunity and infection can result in renal insufficiency, however, decreased complement levels and biopsy-proven TMA in the setting of stable SLE and treated infection should prompt the consideration of aHUS. There have been some successes in treating this entity with eculizumab, a C5a blocker. While this medication's safety during pregnancy is not established, in morbid situations such as the case described, it can be considered as an option.

Supplement: This project was approved by the Duke University Institutional Review Board.

Funding: This work was supported by the National Institutes of Health (R13AR070007).

Disclosure statement: The authors have declared no conflicts of interest.

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