CASE REPORT

A complicated multisystem flare of systemic lupus erythematosus during pregnancy

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SUMMARY

We report a case of systemic lupus erythematosus (SLE) in a young woman who became pregnant amid a severe flare. She continued to have active disease in the face of aggressive treatments complicated by several side effects of immunosuppressive drugs including recurrent sepsis and gestational diabetes. Her fetus was at risk for congenital heart block during the second and third trimesters. Despite an extremely guarded prognosis, she delivered a healthy baby girl. This case highlights the complexities of SLE management during pregnancy. We discuss the therapeutic options available in pregnancy, and highlight the importance of cross-specialty multidisciplinary care in these women.

BACKGROUND

Approximately 6% of women of childbearing age in high-income countries are affected by chronic kidney disease.¹ Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women in their reproductive years,² but does not affect fertility,³ and so these women commonly become pregnant. Sixty per cent of patients with SLE will go on to develop lupus nephritis (LN) and this carries a worse prognosis in terms of maternal and fetal morbidity and mortality.⁴ Owing to the toxicity and teratogenicity of many conventional lupus therapies, treatment of disease flare during pregnancy is challenging.

We present a case of multisystem lupus flare during pregnancy, including a concern for neonatal lupus. This case highlights the therapeutic options available during pregnancy, the multiple side effects of different immunosuppressants, and the importance of cross-specialty multidisciplinary care of these complex patients.

CASE PRESENTATION

In October 2014, a 26-year-old Sudanese woman presented to her general practitioner (GP) with a rash and a 10-month history of hair loss. She had suffered an intrauterine death at 39 weeks' gestation 1 week prior to seeing her GP, having previously had a successful pregnancy in 2010. She was reviewed by dermatology in January 2015 who made a clinical diagnosis of discoid lupus affecting her scalp, face and hands, and was treated with a short course of oral prednisolone (30 mg/day, reducing by 5 mg/week). Antinuclear antibodies were found to be positive at this time (1:2560) with a double-stranded DNA (dsDNA) level of 483 u/mL. She was seen by rheumatology in May 2015 who noted a persistent discoid lupus rash only, and so

she did not initially fulfil the American College of Rheumatology (ACR) criteria for SLE. However, cervical lymphadenopathy (reactive on biopsy), with low complement levels and a positive anti-Smith antibody, was also demonstrated at that clinic, and so she started hydroxychloroquine (HCQ; 200 mg twice daily) in June 2015. In addition, anti-Ro antibodies were positive, and an anti-phospholipid screen was negative (including anticardiolipin antibodies, β -2 glycoprotein antibodies and a lupus anticoagulant). White cell count and renal function were normal and there was no significant proteinuria at that time. By July 2015, dsDNA titres had risen sharply (791 u/mL), with persistent low complement levels, 3+ blood 4+ protein on urine dipstick and a urine protein:creatinine ratio of 157 mg/mmol, but with normal renal function. However, she travelled back to Sudan for the summer, where she stopped taking HCQ, and was not seen again until late September 2015 when she was restarted on oral prednisolone (30 mg per day) by rheumatology and referred urgently to nephrology. After renal review in October, she was started on 500 mg twice daily of mycophenolate mofetil (MMF) with explicit counselling to avoid pregnancy and use contraception. HCQ was also restarted (at 200 mg twice daily) and oral steroids were stopped. A renal biopsy was performed in November 2015 which showed class III (A) +V LN. A fall in serum creatinine on the day of the biopsy provoked a pregnancy test, which was positive. In view of this, but with active disease both serologically and on biopsy, MMF was stopped, and she was treated with two doses of intravenous methylprednisolone (500 mg per dose) and started on tacrolimus (2 mg twice daily) and prednisolone (20 mg/day). Owing to a low thiopurine methyltransferase level (50 mU/L), azathioprine was started at a dose of 50 mg per day. This was temporarily stopped 2 weeks later after a transient fall in white cell count, but subsequently cautiously restarted. A dating scan in mid-December established that she was 11⁺² weeks pregnant. Table 1 summarises the blood and urine investigation results.

In January 2016, she presented to the renal rapid assessment unit with an exacerbation of skin lesions, and with clear evidence of clinically and serologically active lupus, her immunosuppression was escalated to 30 mg daily of oral prednisolone, 75 mg daily of azathioprine and 3 mg twice daily of tacrolimus. In February 2016 (at 17⁺⁵ weeks' gestation), she was admitted with purulent exudate and crusting from her skin lesions, and also

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Table 1 Summary of investigations

	dsDNA (units/mL, 0–30)	uPCR (mg/mmol)	SCr (μ mol/L)	C3 (g/L, 0.70–1.70)	C4 (g/L, 0.16–0.54)	CRP (mg/L)
September 2015 (Pre-pregnancy)	450	272	56	0.44	0.07	0.36
November 2015 (2 weeks after biopsy)	461	248	50	0.51	0.11	0.6
Admission February 2016 (17 weeks' gestation)	78	594	48	0.80	0.16	42.3
Admission March 2016 (21 weeks' gestation)	83	446	46	0.81	0.20	63.3
Delivery (34 weeks' gestation)	100	223	55	1.26	0.20	49.0
Five months postpartum	86	183	55	1.06	0.22	5.5

dsDNA, double-stranded DNA; SCr, serum creatinine; uPCR, urine protein:creatinine ratio.

appeared systemically unwell with a fever of 38°C and a tachycardia of 120 bpm. Skin swabs taken during the previous week had grown methicillin-resistant *Staphylococcus aureus* (MRSA). Sepsis was therefore attributed to this and treated with intravenous vancomycin and topical mupirocin. In view of newly impaired glucose tolerance, tacrolimus was stopped, prednisolone dosing was reduced to 20 mg daily, and azathioprine and HCQ were continued at the same doses. To augment therapy for active lupus, intravenous immunoglobulin (IVIG) was administered at 0.4 g/kg per day for five doses. Fortunately, she remained normotensive with normal renal function throughout. Although she temporarily improved and was discharged, she was readmitted in March 2016 with a similar presentation and treated again with intravenous antibiotics, further IVIG (0.4 g/kg per day for five doses), and the dose of prednisolone was increased back to 30 mg daily. Topical therapies included coal tar, white soft paraffin, chlorhexidine/neomycin nasal cream and chlorhexidine washes (see figure 1).

Fetal heart rate was measured twice per week, and fetal ECGs were performed fortnightly during this period. They showed inflammation (increased echogenicity of the myocardium at the atrioventricular junction and outflow tracts) and, although fetal heart rate was normal throughout, on one occasion there was an increased mechanical atrioventricular interval (160 ms) suggesting first-degree heart block. These confer an increased risk of complete heart block (CHB). In April 2016, insulin and gliclazide were required to control her gestational diabetes. She required further IVIG (0.4 g/kg per day for five doses) in May 2016 for active skin lesions and MMF (500 mg twice daily) was restarted in the third trimester for disease control. In late May

2016, she was readmitted at 33 weeks' gestation with otitis externa. Swabs grew both MRSA and yeast.

DIFFERENTIAL DIAGNOSIS

The diagnosis of SLE with severe renal and cutaneous involvement was clear in this woman. However, when she was admitted in February 2016 with an escalation of skin disease, it was not initially apparent whether this represented infection within her known discoid lupus lesions or cutaneous flare (particularly with ongoing active nephritis). Empirical treatment was therefore given to cover both.

TREATMENT

Initially, IVIG was chosen as adjuvant therapy to azathioprine and corticosteroids for treating LN and cutaneous flare, as we were reluctant to increase immunosuppression in the face of significant infection. While MMF could have been considered from the second trimester, we decided against this. In addition, there was the issue of gestational diabetes to contend with, which may have been exacerbated by additional steroids or the use of calcineurin inhibitors. Subsequently, in the third trimester, we started MMF due to the need to control ongoing active disease.

OUTCOME AND FOLLOW-UP

On 1 June 2016 at 34 weeks' gestation, she had induction of labour for worsening lupus, with a subsequent spontaneous vaginal delivery of a healthy 2.2 kg baby girl. The MMF dose was increased to 750 mg twice daily, and oral prednisolone and HCQ were continued postpartum. Six weeks postpartum, she received two doses of intravenous rituximab (1 g) 2 weeks apart. She is clinically stable, with improving skin lesions and in partial renal remission, and this has allowed the oral prednisolone to be weaned at 5 mg every 4 weeks. Glucose tolerance has now been restored, therefore enabling cessation of gliclazide and insulin. Owing to the lack of data of MMF in breast feeding, she was counselled against breast feeding.

DISCUSSION

Lupus in pregnancy

The recent PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study of 385 patients, excluding those with active nephritis, demonstrated that 81% of pregnancies in women with inactive or stable mild-moderate disease were uncomplicated.⁵ A meta-analysis of 2751 women with SLE showed that those with active nephritis had an increased risk of maternal hypertensive disorders and premature birth.⁴ Furthermore, it has previously been shown that SLE flare is more common in patients with active disease at the time of

Figure 1 Infected discoid lupus lesions on presentation in March 2016.

conception.⁶ A 6-month period of disease quiescence prior to pregnancy is therefore recommended.⁷

Lupus evaluation and treatment during pregnancy

During normal pregnancy, there is a 50% increase in renal blood flow, with a subsequent increase in glomerular filtration rate and reduction in serum creatinine.⁸ An increase in physiological urine protein excretion (up to 300 mg per day) can also be noted. De novo or worsening pre-existing chronic hypertension, and increasing proteinuria during pregnancy are a source of anxiety. Differentiating LN flare from hypertensive disorders of pregnancy, for example, pre-eclampsia (PET), can be challenging, but is important as treatments are different. A dynamic increase in serological lupus markers, with decreased complement levels, thrombocytopaenia, neutropaenia and other organ involvement, would support active lupus but is not always apparent. Biomarkers such as placental growth factor may help to distinguish PET superimposed on pre-existing renal disease.⁹ HCQ is safe in pregnancy, well tolerated and its discontinuation may lead to disease flare.^{10–13} It should therefore be continued during pregnancy.¹⁴ Azathioprine is also safe and should be considered in treatment regimens prior to conception, along with aspirin. Steroids are often used in pregnancy as they are not associated with congenital abnormalities,¹⁵ but can be associated with premature rupture of membranes, preterm delivery and maternal sepsis.¹⁶ Tacrolimus is safe in pregnancy,¹⁷ and breast feeding,¹⁸ and may be a useful alternative or adjunctive therapy for LN flare during pregnancy.¹⁹ Relevant to this case is that both steroids and tacrolimus can cause impaired glucose tolerance and gestational diabetes.^{20–21} This led to tacrolimus being stopped in our patient despite the fact she had active disease. Rituximab has been used successfully in the treatment of LN in non-pregnant patients,²² and there are increasing reports of it being successfully used during pregnancy to treat both haematological and autoimmune conditions.²³ However, it crosses the placenta, lymphopaenia has been reported in neonates and its long-term effects are unknown, and so it should not currently be recommended during pregnancy unless the risks of the underlying disease to the mother warrant its use. Cyclophosphamide and MMF are both teratogenic.¹⁴ Women of childbearing age should have a pregnancy test prior to starting MMF, and be advised not to conceive while taking MMF.²⁴ However, while the teratogenicity of MMF exposure during the first trimester has been confirmed,²⁵ there are no reports on problems from exposure limited to the second or third trimesters. Furthermore, organogenesis is complete by the end of the first trimester, and so the risk-benefit analysis favoured our use of MMF in the third trimester in this case.

There is an absence of firm evidence for the use of IVIG to treat SLE, although it may be a useful maintenance therapy. It should also be considered during a flare, particularly when other therapies have failed, or the patient is too unwell for other immunosuppression, or where concurrent infection is suspected or proven as with our case.²⁶ A case series of 12 patients has previously shown success with the use of IVIG to treat lupus in pregnancy, including patients with evidence of renal involvement.²⁷

Neonatal lupus

The incidence of CHB in the offspring of mothers with antibodies against Ro and La ribonucleoproteins is ~1–2%,^{28–29} with a 17% risk of recurrence in subsequent pregnancies.³⁰ This carries a significant long-term risk of conduction abnormalities and cardiomyopathy for the affected child.^{31–32} HCQ may

reduce the risk of cardiac manifestations of neonatal lupus in anti-Ro-positive mothers and is actively recommended in women with LN before and during pregnancy.^{33–34} However, until the results of the 'Preventive Approach to Congenital Heart Block With Hydroxychloroquine' (PATCH) study are published, we still lack prospective data. There have been case reports of IVIG treating CHB in neonatal lupus but this was not substantiated in two prospective trials,^{35–36} although the doses used in these trials may have been too low.²⁶ It is possible that in our case, IVIG prevented progression from echogenic endocardium to CHB.

Specialist multidisciplinary care

The UK National Institute for Health and Care Excellence (NICE) recommends that all pregnancies where the mother has pre-existing medical conditions or risk factors require additional care.³⁷ Multidisciplinary input from a team of nephrologists, obstetric physicians, obstetricians, rheumatologists, dermatologists, infectious disease physicians and fetal cardiologists, in addition to excellent midwifery and nursing care, with close weekly monitoring of our high-risk patient, resulted in a good outcome. Pre-pregnancy counselling improves knowledge and changes in behaviour prior to pregnancy,³⁸ which may help to reduce adverse events. In women with chronic kidney disease, it offers an invaluable opportunity to optimise blood pressure and proteinuria, and alter teratogenic medications, and it should be routinely offered to all women with pre-existing medical conditions.^{39–40}

In summary, SLE is a complex multisystem autoimmune disease, the treatment of which can be challenging due to the potential toxicity of several of the routinely used medical treatments. These issues are often further augmented during pregnancy. Close monitoring and multidisciplinary care of these patients is important to maximise the chance of favourable outcomes for mother and baby.

Learning points

- Multidisciplinary specialist care is imperative for pregnant patients with systemic lupus erythematosus (SLE).
- Women with SLE should ideally undergo pre-pregnancy counselling with a minimum 6-month period of quiescent disease prior to pregnancy.
- Hydroxychloroquine, azathioprine, tacrolimus, corticosteroids and intravenous immunoglobulin (IVIG) are considered safe throughout pregnancy and can be used in the management of patients with SLE. Mycophenolate mofetil and cyclophosphamide are not safe in the first trimester and are generally to be avoided in pregnancy. Rituximab has been used in pregnant patients with severe lupus with promising results but the safety profile is not yet confirmed.
- Neonatal cardiac lupus causing complete heart block in the fetus is a rare complication in women with positive Ro antibodies. Hydroxychloroquine and IVIG may be beneficial in this circumstance.

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