

CASE REPORT OPEN ACCESS

# New Diagnosis of Lupus Nephritis in the Third Trimester—A Case Report

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## ABSTRACT

New-onset lupus nephritis (LN) poses a diagnostic and management challenge during pregnancy. This is more pertinent in the indigenous population, where the prevalence is higher, and the clinical phenotype tends to be more severe. We report the case of a 30-year-old G3P2 indigenous female, living in remote Queensland, with a late presentation of nephrotic syndrome at 30 weeks gestation. A clinical diagnosis of Class V LN was made without a kidney biopsy due to maternal and foetal risk, and she was empirically treated with steroids and disease-modifying agents to good effect. She remained normotensive with appropriate foetal growth and delivered a healthy male infant at 37 weeks. A renal biopsy taken 9 weeks after commencement of therapy demonstrated Class II LN, likely representing a resolving flare in the presence of improved clinical symptoms.

## 1 | Introduction

Systemic lupus erythematosus (SLE) is one of the most prevalent autoimmune diseases encountered in pregnancy [1]. A new diagnosis of SLE during pregnancy commonly manifests as lupus nephritis (LN) and severe thrombocytopenia, with a higher prevalence of nephrotic syndrome compared to the non-pregnant population [2]. This poses a difficult diagnosis during pregnancy due to an overlap of clinical phenotype with other complications such as pre-eclampsia, and limitations in the ability to perform a kidney biopsy, particularly in the third trimester [3]. Flares of lupus are concerning during pregnancy due to significant complications, including hypertension and pre-eclampsia, worsening of renal impairment and thrombosis [4]. Management options remain limited to medications without teratogenic effects or breastfeeding restrictions [1]. It also predicts unfavourable foetal outcomes, including miscarriage, growth restriction and prematurity, with a recommendation for close monitoring of both the mother and foetus during the pregnancy [5]. Therefore, it is

imperative to have a correct diagnosis and prompt management during pregnancy to optimise both maternal and foetal outcomes.

## 2 | Case Presentation

An Indigenous female in her 30s was transferred to a tertiary hospital from a regional centre at 30 weeks pregnant with concerns of severe lower limb pitting oedema in the preceding month. There was evidence of a new malar rash and an erythematous maculopapular rash over her shoulders and chest. Although there was no family history, she was noted to have a positive antinuclear antibody (ANA) and extractable nuclear antigen (ENA) SS-A in 2017, without follow-up at that time. She had two previous uncomplicated pregnancies leading to the delivery of live infants at term. She had no other medical diagnoses and was not on any medication.

On physical examination, she was normotensive at 113/73. She had evidence of significant lower limb pitting oedema to the

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level of her umbilicus, without any evidence of pulmonary oedema on auscultation. There were normal reflexes and no significant clonus. The laboratory results were as follows: a spot urine protein–creatinine ratio (PCR) of 834 g/mol, serum albumin of < 15, creatinine of 82  $\mu\text{mol/L}$  and eGFR of 83 mL/min. A clinical diagnosis of LN was made based on haematuria, positive ANA (1:160 homogenous), raised anti-dsDNA (> 90 IU/mL) levels and hypocomplementemia with a C3 of 0.3 g/L and a C4 of 0.1 g/L (Table 1). She was noted to be anti-SSA/Ro positive. Antiphospholipid antibodies were negative. Obstetric ultrasound showed an estimated foetal weight (EFW) in the 74th centile, with normal dopplers and no evidence of growth restriction.

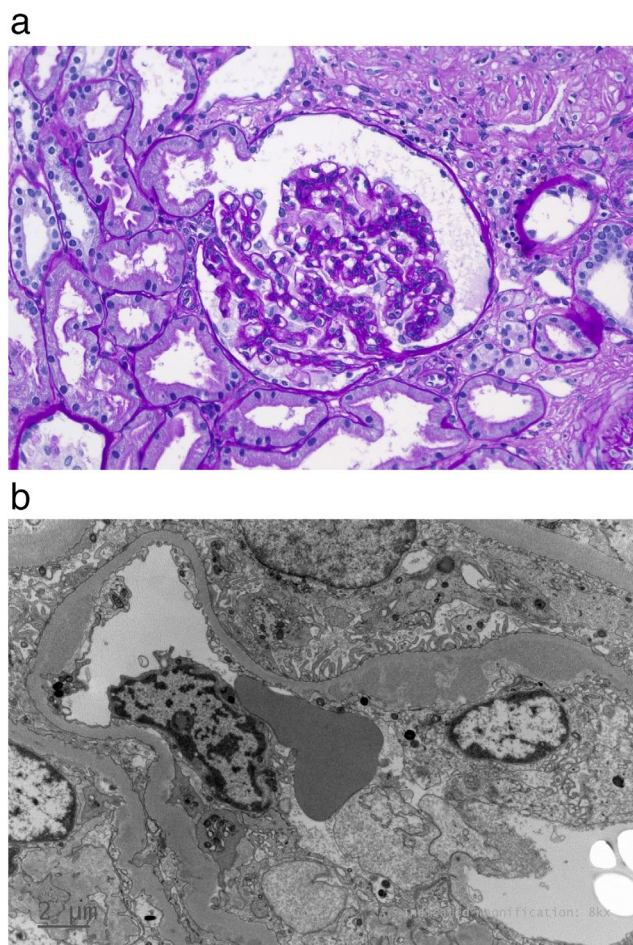
Her nephrotic syndrome was treated with bolus intravenous frusemide 40 mg three times a day, albumin and intermediate dose of enoxaparin 70 mg (1 mg/kg) daily. Given the maternal and foetal risks in the setting of anticoagulation and her current gestation, a kidney biopsy was not performed. Instead, Class V LN was diagnosed on clinical and serological findings. She went on to receive three doses of IV 500 mg Methylprednisone, then 50 mg oral prednisone, and was treated with hydroxychloroquine 200 mg daily, tacrolimus 4 mg twice daily and azathioprine 50 mg daily.

She continued to be closely monitored with weekly soluble fms-like tyrosine kinase 1 to placental growth factor (SFLT1/PIGF) ratio and cardiocographs (CTGs). Although she remained normotensive with appropriate foetal growth, she was noted to have a high SFLT1/PIGF ratio of 194 at 36 weeks concerning the development of pre-eclampsia and delivered a healthy male infant weighing 2440 g at 37 weeks via repeat elective Caesarean section. She commenced breastfeeding postpartum, with a reduction in her prednisone from 50 to 30 mg to facilitate this.

She went on to get a renal biopsy 2 weeks postpartum. The light microscopy demonstrated a mesangial proliferative appearance consistent with likely treated Class II LN (Figure 1a), and electron microscopy demonstrated several large subendothelial electron-dense deposits with variably sized subepithelial deposits with focal podocyte effacement and endothelial tubular reticular inclusions consistent with a mild Class III LN (Figure 1b). She went on to have a relapse at 2 months postpartum in the setting of missed medications, which responded to an increase in her prednisone dose. At 3 months postpartum, she was transitioned from azathioprine to mycophenolic acid as she was no longer breastfeeding. At 5 months postpartum, she had a further relapse in the setting of medication side effects leading to self-cessation. This responded to reinitiation of medications and an increase in prednisone dose. Ongoing telehealth engagement became challenging, and she was linked with a local nurse navigator and renal service. She is currently managed on a weaning dose of prednisone 10 mg, tacrolimus 3 mg twice daily, mycophenolate mofetil 1000 mg twice daily and hydroxychloroquine 200 mg daily with preserved renal function and minimal albuminuria.

### 3 | Discussion

This case showcases the successful management of a new diagnosis of LN in the third trimester of pregnancy without a renal biopsy. SLE is a chronic, multi-system disease characterised by the loss of tolerance to self-antigens resulting in autoantibody



**FIGURE 1** | Renal histology. (a) Light microscopy demonstrating a mesangial proliferative appearance representing likely treated Class II lupus nephritis (PAS 200 $\times$ ). (b) Electron micrograph demonstrating several large subendothelial electron-dense deposits suggesting mild Class III lupus nephritis (8000 $\times$  magnification).

production and tissue damage, which can result in significant morbidity and reduction in quality of life [6]. The incidence is higher in females compared to males [1]. The disease phenotype has been shown to be more severe in Indigenous Australians, likely contributed to by environmental and genetic factors, as well as difficulties with healthcare access and delayed presentation [7]. However, there is a lack of research in this area, which poses difficulties in management [7].

This patient presented with nephrotic syndrome—characterised by > 3 g/day of proteinuria with hypoalbuminaemia and oedema. It is difficult to determine whether the aetiology is pregnancy-related or a new diagnosis of glomerulonephritis [8]. Although urinary protein excretion can increase in pregnancy due to a combination of glomerular hyperfiltration and increased glomerular basement permeability, nephrotic range proteinuria does not occur in normal pregnancy physiology [9]. Pre-eclampsia can certainly be a consideration with proteinuria and acute kidney injury; however, the absence of hypertension made this less likely, as seen in Table 2 [10]. Additionally, the soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PIGF) ratio were negative. This test has been shown to have a high negative predictive value to rule out developing pre-eclampsia within 7 days [11]. This determination allowed for the

**TABLE 1** | Timeline of results during admission, in peripartum phase, at time of renal biopsy, post-treatment and follow-up after 1 year.

	Admission	Peripartum (4 weeks postadmission)	Renal biopsy (2 weeks postpartum)	Post-relapse and treatment (3 months postpartum)	Follow-up (18 months later)
Na (mmol/L)	136	138	140	140	141
K (mmol/L)	3.5	4.7	4.6	4.0	3.9
HCO <sub>3</sub> (mmol/L)	21	22	26	28	25
cCa (mmol/L)	1.67	8.9	2.53	2.36	2.26
PO <sub>4</sub> (mmol/L)	1.17	1.34	1.51	1.12	1.01
Albumin (g)	<15	18	22	28	41
Ur (mmol/L)	5.8	8.9	12.1	4.7	3.3
Creatinine (μmol/L)	82	50	87	49	68
eGFR (mL/min)	83	>90	77	>90	>90
Hb (g/L)	105	96	104	110	146
WCC (10 <sup>9</sup> /L)	6.9	13.6	8.2	9.4	5.5
Lymphocytes (10 <sup>9</sup> /L)	0.96	1.42	3.57	3.85	2.18
Platelets (10 <sup>9</sup> /L)	196	229	404	316	313
Urine MCS					
WCC: white cell count (×10 <sup>6</sup> /L)	WCC > 500			WCC 30	WCC < 10
RBC: red cell count (×10 <sup>6</sup> /L)	RCC 250			RCC 20	RCC 33
Epi: epithelial (×10 <sup>6</sup> /L)	Epi > 50			Epi > 50	Epi < 10 1+ protein
Urine PCR (g/mol)	834	794 Timed 8300 mg/24 h	110 Timed 635 mg/24 h	82	—
Urine ACR (mg/mmol)	—	—	58 Timed 338 mg/24 h	45	5.8
Anti-dsDNA (IU/mL)	>90	12		22	22
Complements (g/L)	C3 0.3 C4 0.1	C3 0.80 C4 0.32		C3 0.9 C4 0.38	C3 1.021 C4 0.254
Tacrolimus level (μg/L)		3.8	7.6	4.3	3.0
sFLT-PIGF ratio	8.8	194			

Abbreviations: anti-dsDNA, anti-double-stranded DNA; cCa, corrected calcium; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HCO<sub>3</sub>, bicarbonate; K, potassium; Na, sodium; PO<sub>4</sub>, phosphate; sFLT/PIGF ratio, soluble fms-like tyrosine kinase 1 to placental growth factor ratio; Ur, urea; urine ACR, urine albumin-creatinine ratio; urine MCS, urine microscopy, culture, sensitivities; urine PCR, urine protein-creatinine ratio; WCC, white cell count.

prolongation of pregnancy for an additional 7 weeks before the decision to deliver was made based on gestation, rising blood pressures and new positivity in this biochemical marker [12].

There is much hesitancy around performing kidney biopsy in pregnancy, particularly after 25 weeks gestation, due to the risk of complications such as peri-renal haematoma, abscess and sepsis [3]. Especially for this patient, the risk of biopsy, including bleeding in the context of anticoagulation in the setting of her nephrotic syndrome and increased thrombotic risk during

pregnancy, was outweighed by the need for a tissue diagnosis. A clinical diagnosis of LN was possible based on her immunological markers, for which she had a score of 14 on the EULAR/ACR (European Alliance of Associations for Rheumatology/American College of Rheumatology) Criteria for the Classification of SLE [13]. Interestingly, her postpartum biopsy revealed Class II LN; however, her presentation with nephrotic syndrome is more in keeping with either Class IV or Class V LN [14]. This would have begun to resolve histologically due to the treatment of the disease for 12 weeks prior to biopsy [14].

**TABLE 2** | The table showcases the difference between pre-eclampsia and lupus nephritis.

	<b>Lupus nephritis</b>	<b>Pre-eclampsia</b>
Onset	Anytime	After 20 weeks
Hypertension	Present or absent	> 140 SBP and/or > 90 DBP
Active urine sediment	Present	Absent
Proteinuria	> 300 mg/day	> 300 mg/day
Acute kidney injury	Possibly	Possibly
Uric acid	Usually low to normal	High
Platelets	Normal or low	Normal or low
Aminotransferase activity	Rarely increased	Frequently increased
Complement levels (C3 and C4)	Normal to low	Normal to high
Anti-dsDNA	High	Negative (or stable)
sFLT-PIGF ratio	Normal	Normal to high

The literature supports her treatment regimen of corticosteroids, hydroxychloroquine, tacrolimus and azathioprine in pregnancy and breastfeeding [1]. It was noted that azathioprine should be used with caution in individuals who are thiopurine methyltransferase (TPMT) deficient, which was tested and ruled out in this patient [15]. Cyclophosphamide and mycophenolate are not recommended as induction agents during pregnancy or breastfeeding [15]. Co-administration of frusemide and albumin has been shown in the non-pregnant population to enhance diuresis and naturesis, particularly in settings of low albumin or impaired renal function [16, 17]. Regardless of a lack of pregnancy-specific data, effective diuresis was obtained in this patient with improvement of her oedema during her hospital admission. Given the severity of the presentation and remoteness of her location, this patient was transferred to a tertiary centre for management, allowing for close collaboration among the multidisciplinary team, including obstetrics, neonatology, obstetric medicine and nephrology to facilitate management and delivery planning.

It is important to note the challenges in managing this patient, particularly as an Indigenous female from a rural area. She required prolonged inpatient admission for management during pregnancy away from her children and community supports, and struggled with medication management and appointment attendance, particularly in the early postpartum period. The involvement of an Indigenous Liaison Officer is vital to bridge the cultural gap and provide culturally appropriate support to Indigenous patients. Additionally, a local nurse navigator providing additional surveillance and support can assist in ensuring adherence to treatment and can be an invaluable asset to providing complex care in rural and remote areas.

#### 4 | Conclusion

This case demonstrates a successful treatment of LN during pregnancy with the delivery of a live early-term infant. The presence of Class II LN in the kidney biopsy alone likely signifies successful treatment during pregnancy and evidence of a resolving flare. This

shows the benefit of a multidisciplinary approach with medical, obstetric and neonatal monitoring, which allowed for the optimisation of maternal and foetal outcomes, as well as approaching the challenges of managing patients in rural and remote communities.

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#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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