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| RESEARCH ARTICLE

Difficult-to-manage Flare up of Lupus Nephritis during Pregnancy with Confusing Laboratory Findings: A Case Report

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| ABSTRACT

The inevitable hormonal shifts in the course of pregnancy serve a huge impact on autoimmune disease activity, especially SLE (Systemic Lupus Erythematosus). Although extensively studied in non-pregnant populations, LN (Lupus Nephritis) becomes challenging to diagnose and treat in the context of pregnancy. This case study explores the flare up of LN (Lupus Nephritis) in a 32-year-old Saudi female, who is previously known to have SLE (Systemic Lupus Erythematosus) with a background of biopsy-proven ISN\RPS Class IV LN (Lupus Nephritis) as a consequence that was recently put into remission, yet followed by a relapse upon conception, giving rise to isolated renal disease with strikingly unusual normal numerical values of inflammatory markers, obscuring the clarity of the diagnosis owing to the overlapping with other similar conditions like preeclampsia and deferral of the vital role of renal biopsy for confirmation and monitoring given the patient is in mid-pregnancy (2nd trimester), forcing the approach to be centered around other alternative parameters and markers rather than invasive monitoring, encouraging a deeper understanding of the nature of these laboratory markers beyond mere results. This patient was successfully managed by steroids course and MMF (Mycophenolate Mofetil) without the need to escalate the immunosuppressive therapy or use potentially teratogenic agents.

| KEYWORDS

Systemic Lupus Erythematosus, Lupus Nephritis, Proteinuria, Acute Kidney Injury, Pregnancy

| ARTICLE INFORMATION

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, multisystem autoimmune disorder. It is marked by a diverse range of clinical manifestations (e.g. rash, arthritis, nephritis, hematologic and neurologic symptoms). Gender-wise, it is more common in females with predominance rates of female: male ~9:1 and typically manifests in females of reproductive age. A recent systematic review and meta-analysis showed prevalence rates of approximately 78.7 per 100,000 in females versus 9.3 per 100,000 in men [2]. Importantly, SLE (Systemic Lupus Erythematosus) has a very minor to no impact on fertility. Most studies demonstrated that in females in whom SLE (Systemic Lupus Erythematosus) is well-controlled, fertility is generally preserved, and normal reproductive potential is retained, aside from cases with impaired fertility on account of cytotoxic treatment with

exhausted ovarian reserve. For example, Velarde-Ochoa et al. note that "fertility in SLE patients is considered normal", except when disease activity or cyclophosphamide exposure cause ovarian damage [1]. Hence, SLE (Systemic Lupus Erythematosus) per se does not preclude conception, patients must only avoid potentially teratogenic drugs and manage disease activity while planning conception beforehand. On the contrary, pregnancy has a substantial impact on SLE (Systemic Lupus Erythematosus) disease activity. One of the reasons is that immune and hormonal shifts during pregnancy can provoke and induce a lupus flare, especially when SLE (Systemic Lupus Erythematosus) is not quiescent at conception. Some studies noted that there is a two-to-three-fold increase in SLE (Systemic Lupus Erythematosus) flares during gestation [3]. Importantly, since the potential for a flare is at its peak when active disease is present at conception, a couple of SRMA (Systematic Reviews and Metanalysis) studies confirm that having SLE (Systemic Lupus Erythematosus) in remission prior to conception enormously lowers flare risk [4]. For instance, achieving clinical remission before pregnancy was associated with roughly a 70% reduction in flare risk [4]. For such reasons, most guidelines highly advise that females should delay gestation until SLE (Systemic Lupus Erythematosus) has been quiescent for at least ≥6–12 months [4]. Yet, despite these measures lupus flares do occur in a significant minority of pregnancies - one systematic review found flares in ~25% of cases – underscoring that pregnancy is a high-risk period even for well-controlled SLE (Systemic Lupus Erythematosus) [4]. In addition, obstetric risks and complications in pregnant patients with SLE, were noted to be much higher than healthy pregnant women. The classic complications include preeclampsia, fetal loss (miscarriage or stillbirth), preterm birth, and IUGR (Intra-Uterine Growth Restriction). Numerical data confirm these associations, for instance, some studies displayed approximately 16% of pregnant SLE (Systemic Lupus Erythematosus) were terminated due to miscarriage or fetal loss, 7.6% went on to develop preeclampsia, 12.7% of live births were complicated by IUGR (Intrauterine Growth Restriction), and preterm delivery occurred in 40% of all births [4]. Moreover, women with SLE (Systemic Lupus Erythematosus) during pregnancy are more prone to C-sections and have a higher chance of their babies experiencing health problems like neonatal lupus soon after birth. Such risks are amplified by lupus-related factors like antiphospholipid antibodies, hypertension and most importantly active lupus nephritis, all of which collectively contribute to increased obstetric complications [5]. Hence, in practice, healthy SLE (Systemic Lupus Erythematosus) pregnancies mandate close monitoring by multidisciplinary care, females are encouraged to attain stable remission before gestation and to continue safe medications like hydroxychloroquine [5]. From all SLE (Systemic Lupus Erythematosus) manifestations, renal deterioration in the form of LN (Lupus Nephritis) is distinctly serious and common. LN (Lupus Nephritis) represents immune-complex glomerulonephritis mediated by active SLE (Systemic Lupus Erythematosus), and it is characterized by high rates of morbidity. Clinically evident LN (Lupus Nephritis) appears in approximately 50-60% of SLE (Systemic Lupus Erythematosus) patients and many more have evidence of renal pathology on biopsy that is consistent with LN (Lupus Nephritis) [6]. A significant percentage of pregnant women with SLE (Systemic Lupus Erythematosus) have a history of LN (Lupus Nephritis). One study analysis stated that about 16–19% of SLE (Systemic Lupus Erythematosus) pregnancies involved active LN (Lupus Nephritis) at conception, and the overall prevalence of any lupus nephritis history in SLE (Systemic Lupus Erythematosus) cohorts is on the order of 40–60% [3]. LN (Lupus Nephritis) histological class as per WHO/ ISN–RPS criteria is a strong predictor of prognosis. While the worst outcomes are observed in proliferative forms (Class III/IV), membranous from (Class V) has a relatively better prognosis [6]. Long term studies have shown that 26% of LN (Lupus Nephritis) patients progress to ESRD (End-Stage Renal Disease) over 10–15 years [6]. The 15-year risk of progression to end-stage renal disease is significantly higher in Class IV lupus nephritis patients, reaching approximately 44%, compared to Class V patients where it is around 20%. Thus, histologic classification via biopsy is critical to guide therapy and counselling [6]. Managing lupus nephritis in pregnancy is demanding and challenging, given the need to balance maternal disease control against fetal safety. Additionally, pregnant females with LN (Lupus Nephritis) are highly vulnerable to developing complications. Furthermore, many LN (Lupus Nephritis) medications including mycophenolate and cyclophosphamide have significant fetal risks or limited safety data. As a result, LN (Lupus Nephritis) constitutes a critical scenario with very limited clinical trials available to guide treatment. This case highlights both the diagnostic and therapeutic challenges during the management of LN (Lupus Nephritis) in a pregnant lady.

2. Case Presentation

2.1 Patient's history

This case report presents to you a 32-year-old Saudi female who has been known to have SLE (Systemic Lupus Erythematosus) for the past seven years. Additionally, this woman has the background of biopsy-proven ISN\RPS (International Society of Nephrology \ Renal Pathology Society) Class IV Lupus Nephritis that was discovered around two years ago following kidney biopsy. She successfully attained clinical remission over the past few months and was on maintenance therapy in the form of MMF (Mycophenolate Mofetil) and low-dose steroids. The patient was counseled against pregnancy and conception was deemed inadvisable until serologies and kidney functions have been stabling for at least 6 months, with the plan of shifting her to a relatively more pregnancy-safe medication in the form of Azathioprine before planned conception, but unfortunately, she lost follow-up. She returned to our facility complaining of progressive facial edema. The patient also reported foamy urine, diffuse joint pain in both knees, elbows and small joints of hands, persistent fatigue, subjective fever and hair loss. She denied any hematuria, change in urine output, appearance of skin rash, bruising, headache, visual changes, seizures, abdominal pain, cough, dyspnea or chest pain. A pregnancy test was ordered as part of the lab work that was done, and it was found to be

positive. The patient was aware of her pregnancy status, with the calculated gestational age to be 17 weeks according to her LMP (Last Menstrual Period). Even so, she did not visit any obstetric or primary care physician during this period, and she did not stop MMF (Mycophenolate Mofetil) either. It is worth mentioning that our patient had prior obstetric complications in the form of three non-consecutive abortions, but no past thromboembolic events. Her current pregnancy course was uneventful in terms of any obstetric complications like bleeding till the time of presentation.

2.2 Physical examination

By examination, the patient was alert, not in any distress or pain, appeared puffy, but not pale nor jaundiced. Her vitals showed blood pressure of 152\95 mmHg, temperature of 36.8, heart rate of 78 and respiratory rate of 12. No malar rash, oral ulcers, or bruising were noticed but she had significant patchy alopecia in her scalp. The abdominal examination was unremarkable with no flank tenderness or signs of ascites. No lymph nodes were detected by palpation. By auscultation there was no friction rub sound, decrease in intensity of breathing and jugular veins weren't distended. Lower limbs showed mild and painless bilateral pitting edema. Joints showed no signs of inflammation such as redness or swelling. Obstetric examination revealed no abnormalities and fetal heart tones were detected by Doppler. Urine examination results indicated heavy proteinuria with no observation of any casts (Table 1).

Parameter	Result	Note
Color	Yellow	-
Appearance	Cloudy	-
Specific Gravity	1.020	-
pH	6	-
Protein	+3	Significant proteinuria (suggesting possible flare)
Glucose	Negative	-
Ketones	Negative	-
Blood	+2	Suggests hematuria
Nitrites	Negative	-
Leukocyte Esterase	Trace	Suggesting mild leukocyturia which could be inflammatory
Urobilinogen	Trace	-
Bilirubin	Normal	-
RBCs	10-15\hpf	Active hematuria with possible glomerular origin
WBCs	3-5\hpf	Mild pyuria which could be non-infectious
Casts	None	Could've supported glomerulonephritis if present
Epithelial cells	Few	Acceptable contamination
Bacteria	None	-
Crystals	None	-

Table 1: results of urine examination.

3. Laboratory results

Comprehensive lab work had to be done, as shown below (Table 2).

Test	Result	Normal Range	Note
Sodium	140 mmol\L	135-145	-
Potassium	4.4 mmol\L	3.5-5.0	-
Chloride	102 mmol\L	98-107	-
Bicarbonate	18 mmol\L	22-29	Low, reflecting metabolic acidosis
BUN	18 mg\dL	7-20	Slightly elevated
Creatinine	1.4 mg\dL	0.5-0.9	High for a pregnant
eGFR	~ 50 mL\min	>90	Correlates with CKD stage G3a
Fasting glucose	85 mg\dL	70-100	-
Calcium	8.9 mg\dL	8.5-10.2	-
Hemoglobin	9.2 g\dL	12-16	Anemia: could be of chronic disease or renal in origin
WBC	$4.2x10^9$\L	4-10	

Platelets	155x10^9\L	150-400	-
MCV	82 fL	80-100	Suggests normocytic anemia
Reticulocytes	1.1%	0.5-2	-
ESR	58	<20	Suggests inflammatory reaction but could be non-specific in pregnants
CRP	8mg\L	<5	Mildly elevated
ANA	Positive: 1:640	-	Titer is significantly positive
Anti ds-DNA	Negative	-	Goes against disease activity
Anti Smith	Positive	-	Specific for SLE
Anti Ro (SSA)	Positive	-	Risk of neonatal lupus
Anti La (SSB)	Positive	-	Risk of neonatal lupus
Lupus Anticoagulant	Negative	-	Making APS less likely
Anticardiolipin	Negative	-	-
B2 Glycoprotein	Negative	-	-
Spot UPCR	2.5 g\g	<0.2	Nephrotic range
24h protein	2.7 g\day	<150	Matches with UPCR
bHCG	Positive	-	Confirms pregnancy status
C3	100mg\dL	90-180	Goes against disease activity
C4	20mg\dL	10-40	Goes against disease activity

Table 2: results of lab work.

4. Management course

This patient was admitted as a case of suspected flare of Class IV LN (Lupus Nephritis), likely relapsing or persistent. Follow-up renal biopsy plays a major role in guiding the treatment of such cases, but it was deferred as this patient was in the 2nd trimester of her pregnancy and her kidney functions weren't rapidly deteriorating. Plus, the whole clinical picture provided enough evidence to support the possibility Class IV LN (Lupus Nephritis) and indicate empiric immunosuppressive therapy tailored to pregnancy. MMF (Mycophenolate Mofetil) was immediately stopped to avoid possible teratogenicity. Regarding blood pressure control in the setting of renal disease, we usually prefer the introduction of ACEi\ARB due to their renal protective properties; however, they carry a serious teratogenic risk during pregnancy, hence they must be avoided, and oral Labetalol had to be used instead. To address her renal disease, IV methylprednisolone was started upon suspicion of autoimmune etiology, in addition to Azathioprine as well, which is known to be relatively safe in pregnancy. When she finished her IV course of methylprednisolone, we shifted her to oral prednisolone. Low-dose Aspirin therapy had to also be initiated as supportive therapy since the patient is at high risk for preeclampsia; this decision was supported by EULAR 2023 (European Alliance of Associations for Rheumatology), which recommends the use of low-dose Aspirin for any pregnant patient with SLE (Systemic Lupus Erythematosus). Serial growth scans and uterine doppler were done for fetal monitoring, as well as fetal echo to exclude cardiac complications of neonatal lupus which could present in the form of bradycardia and AV block or even myocarditis on rarer occasions. Response was noted in around 3-4 weeks by reduction of proteinuria and normalization of serum creatinine. Markers of disease activity like C3, C4 and Anti ds-DNA remain unchanged. Monthly UPC ratio, urine analysis and serum creatinine while monitoring blood pressure were all planned and conducted while the patient is maintained on Azathioprine and a tapering dose of steroids throughout the pregnancy with results shown below (Table 3). Since no obstetric indication was found, and her condition was stabling, vaginal delivery was planned at term while following up as a high-risk pregnancy. She successfully delivered a full-term 2.7kg healthy male with no cardiac involvement or any other complications of neonatal lupus.

First UCP %	2nd UCP %	3rd UCP %	4th UCP %	5th UCP %	6th UCP %
2.5 g\g	1.7 g\g	1.3 g\g	0.5 g\g	0.35 g\g	0.25 g\g

Table 3: showing progressive reduction in proteinuria in response to therapy.

5. Discussion

While this patient has already fulfilled the EULAR\ACR (European Alliance of Associations for Rheumatology\American College of Rheumatology) 2019 criteria for diagnosis of SLE (Systemic Lupus Erythematosus) and has evident signs of renal disease supported by previous renal biopsy, the diagnosis of LN (Lupus Nephritis) continues to be elusive as the patient's markers of disease activity like C3, C4 and Anti ds-DNA were within normal limits, which obviously argues against LN (Lupus nephritis) activity and could point towards an alternative explanations like preeclampsia, which could also lead to a similar presentation. While C3, C4 and Anti ds-DNA are sensitive markers for the activity of SLE (Systemic Lupus Erythematosus), they could still be unusually normal during flares, especially in cutaneous or musculoskeletal disease, but this has been found to be rare in isolated renal disease when compared to other similar case reports [9]. Few keys go against preeclampsia, including symptoms of disease activity like joint pain and above all the gestational age, as preeclampsia usually onsets after 20 weeks, when the placenta is

already formed, due to the theoretically placental-related etiology of preeclampsia. Yet sometimes preeclampsia has an earlier onset than 20 weeks. And while the identification of RBC casts may constitute compelling evidence of LN (Lupus Nephritis), their absence does not exclude the possibility of a glomerular disease at all [8]. Despite the fact that the response to immunosuppressive therapy is a credible basis for the assumption of LN (Lupus Nephritis), the gold standard remains the renal biopsy [7]. Adversely, this is one of the obstacles for diagnosis of LN (Lupus Nephritis) within the scope of pregnancy as this invasive, yet reliable method may not be applicable if the renal functions are not rapidly reclining and should be postponed postpartum [8]. Usually, the most sensitive method to confirm the root cause of such a case, monitor disease activity and guide treatment is the renal biopsy. But in such a scenario, we may rely on non-invasive strategies like monitoring proteinuria and markers of SLE (Systemic Lupus Erythematosus) activity [8]. While biopsy could still serve as an ideal postpartum tool to determine a definitive etiology, it became of less importance in this case, since the patient has already achieved remission anyways, lacking any solid indication to proceed with the biopsy, like persistent proteinuria or unstable kidney function. All these diagnostic challenges demand a multidisciplinary approach involving rheumatologists, nephrologists and obstetricians. Difficulties and challenges are not exclusive to diagnosis, but they also involve treatment, as cases of LN (Lupus Nephritis) require management that is tailored to the pregnancy, including prescribing proper medications for the concern of fetal safety. Some immunosuppressive agents like MMF (Mycophenolate Mofetil) and Cyclophosphamide and even antihypertensive medications like ACEi\ARB which are beneficial in non-pregnant patients with renal hypertension all have been deemed teratogenic [9]. Another major concern in this case was the positivity of both antiRo and antiLa, which are linked to neonatal lupus and AV block, which pressed the need for fetal monitoring by echo [9]. Gradual taper of prednisolone postpartum and stoppage of Azathioprine 3-6 months post-partum while continuing Hydroxychloroquine indefinitely was a reasonable plan since remission was successfully sustained. Remission can be confirmed according to EULAR (European Alliance of Associations for Rheumatology) and KDIGO (Kidney Disease: Improving Global Outcome) by maintaining normal creatinine, inactive urinary sediment, normal C3, C4 and Anti ds-DNA while extra-renal symptoms are suppressed [8]. Even though goals of treatment in the form of induction and maintenance were met, in other circumstances if the therapy had failed to achieve this, escalation of the medical treatment was going to be challenging, highlighting the literature gaps and lack of evidence for effectiveness of immunosuppressive therapies in treatment of LN (Lupus nephritis) during pregnancy. This literature gap forces the escalation of immunosuppressive therapy to be a risk-benefit-based clinical decision, especially with the limited data we have about biological therapies like Rituximab and the presence of a safety ceiling for the dose of Azathioprine, being 2mg\kg\d, which could be insufficient in severe LN (Lupus Nephritis) cases. Higher doses of Azathioprine and the introduction of Cyclophosphamide when encountering life threatening cases can still be justified though, especially after the first trimester, ignoring all risks which may even include impairing future fertility by damaging the ovarian reserve [8]. The pursuit of specific strategies to address these problems is a matter of future research and scientific progress.

6. Conclusion

The principal outcome observed from this study is that the management of such cases brings many diagnostic and therapeutic challenges that can only be overcome by a multidisciplinary approach between rheumatologists, nephrologists and obstetricians. Another major highlight is the significant importance of tailoring the management of Lupus Nephritis to the pregnancy; it might demand non-invasive monitoring of renal disease activity, deferring the role of renal biopsy and in other words forcing us to rely on other parameters like C3, C4 and Anti ds-DNA to differentiate LN (Lupus Nephritis) from other etiologies like preeclampsia and guide response to therapy. However, it shouldn't come as surprising that some flares may exist with normal markers of disease activity, hence differentiating criteria between LN (Lupus Nephritis) and conditions like preeclampsia still requires further research. Additionally, literature gaps regarding optimal choice when escalating treatment in severe LN (Lupus Nephritis) during pregnancy do exist, forcing clinicians to make risk-benefit-based decisions. Finally, this case highlights the value of planned pregnancy to prevent such progression in the first place.

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