Postpartum nephrotic syndrome related to new onset of systemic lupus erythematosus: A case report

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A B S T R A C T
Postpartum nephrotic syndrome in a pregnant woman with rheumatoid arthritis in long-standing remission is rare. Systemic lupus erythematosus can remain undiagnosed, especially in the absence of clinical manifestations. We present the case of a 34-year-old woman (gravida 2, para 1) who underwent a lower-segment cesarean section at 34 weeks and 6 days of gestation because she had developed preeclampsia and nephrotic syndrome. The concomitant presence of significant hypoproteinemia, hypoalbuminemia, uremia, elevated creatinine serum levels, hyperuricemia and hypertriglyceridemia is indicative of impaired renal function and nephrotic syndrome. This woman was diagnosed with systemic lupus erythematosus nephritis. It is imperative for clinicians to investigate the exact pathophysiological causes of nephrotic syndrome with onset in the puerperium and implement the appropriate therapeutic regimens.

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1. Introduction
Systemic lupus erythematosus (SLE) is a chronic immune-mediated inflammatory disease [1]. Women, especially those of reproductive age, are significantly more affected than men [2]. Renal disease from SLE is associated with obstetric complications, such as preeclampsia and preterm birth [3–5]. Among women with active SLE nephritis, the incidence of preeclampsia and eclampsia may reach 66% [6]. Hypertension, proteinuria and a decline in renal function can be present in preeclampsia, making differentiation of lupus nephritis from preeclampsia difficult, as these conditions can coexist [6]. The diagnosis of lupus nephritis is associated with the presence of decreasing complement levels and increasing double-stranded DNA (dsDNA) antibody levels, in addition to proteinuria and new-onset high arterial blood pressure [7]. We present a challenging and very rare case of a pregnant woman with sudden onset in the third trimester of nephrotic syndrome secondary to new onset of SLE and hypertension.

2. Case report
A 35-year-old Caucasian woman (gravida 2, para 1) at 34 weeks plus 6 days of gestation, according to her last normal menstruation date and nuchal translucency scan, was admitted to the department dealing with high-risk pregnancies with significant edema in both legs, face and neck. On admission, her systolic arterial blood pressure was 140 mmHg and her diastolic arterial blood pressure was 90 mmHg, while her initial booking blood pressure at 6 weeks of gestation had been 100 mmHg over 70 mmHg. Her body temperature was 36.6 °C (or 97.88 °F). Moreover, her medical history included rheumatoid arthritis without any medication for the last three years, which had been diagnosed 6 years previously (at age 29). She was on levothyroxine sodium 50 μg once daily per os due to gestational hypothyroidism.

At 34 weeks plus 6 days of gestation she went into spontaneous preterm labor and, taking into account her previous cesarean section, it was decided that a cesarean section should again be performed. No intraoperative complications occurred. She gave birth to her first child four years earlier by elective cesarean section at 37 weeks plus 5 days of gestation, due to oligohydramnios and fetal growth restriction. Her first child was a healthy girl weighing 2200 g. Her initial laboratory testing included a full blood count, serum electrolytes, liver enzymes, urea and creatinine, urinalysis and coagulation markers. All were within the normal range, except for serum creatinine, which was 1.5 mg/dl (normal values 0.6–1.1 mg/dl).

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38.2 °C (or 100.76 °F) that subsided with acetaminophen, and she developed bilateral significant edema from her feet to her thighs. Laboratory testing on the second postoperative day indicated anemia [hematocrit 27% (normal values 36%–46%) and hemoglobin 9.3 g/dl (normal values 12–16 g/dl)], hypoproteinemia [4.3 g/dl (normal values 6.4–8.7 g/dl)], hypoalbuminemia [2.1 g/dl (normal values 3–5 g/dl)], uremia [67.2 mg/dl (normal values 2.4–5.7 mg/dl), elevated creatinine serum levels [1.6 mg/dl (normal values 0.6–1.1 mg/dl)], hyperuricemia [7.9 mg/dl (normal levels 2.4–5.7 mg/dl)] and hypertriglyceridemia [563 mg/dl (normal values <200 mg/dl)], HELLP syndrome was excluded, because her liver tests and thrombocytes were constantly normal, ranging from 180 K/μl to 334 K/μl for platelets (normal range 150–450 K/μl), from 16 U/l to 34 U/l for AST (normal levels <32 U/l), from 6 U/l to 7 U/l for ALT (normal range < 33 U/l) and from 9 U/l to 29 U/l for γ-GT (normal levels 5–36 U/l). Therefore, she was referred for nephrological assessment. The nephrologists suggested the initiation of tinzaparin sodium 3.500 anti-Xa IU intramuscularly, methylpredniso 250 mg four times orally and intravenous human albumin at a dosage of 50 mg three times daily followed by 20 mg of intravenous furosemide after each dose of albumin, so as to improve edema by diuresis and natriuresis. Furthermore, she had daily determination of fluid balance, sodium dietary restriction and measurement of body weight. The patient’s arterial blood pressure remained consistently above 140/90 mmHg and her urea levels were constantly >8 mg/dl. Furthermore, her hematocrit remained constantly low during her stay in hospital, while urinalysis and 24-hour urine testing showed significant microscopic hematuria and proteinuria. The patient had respiratory alkalosis due to tachypnea [pH 7.515 (normal values 7.35–7.45), pO2 81.2 mmHg (normal values 80–100 mmHg), pCO2 24.5 mmHg (normal values 35–45 mmHg)] and HCO3− 22.3 mEq/l (normal values 21–28 mEq/l). Because she had persistent pyrexia (38.5°C) and complained of shortness of breath, blood and urine cultures, abdominal ultrasonography, Doppler venous ultrasonography of the legs, as well as thorax, abdominal and pelvic spiral computed tomography (CT) were undertaken in order to exclude deep-vein thrombosis, pulmonary embolism and septic pelvic thrombophlebitis. All these tests were negative, except for the abdominal ultrasound and thorax spiral computed tomography, which both showed bilateral pleural effusion, especially on the right, with possible atelectasis of the right lower lobe of the lung.

Because of the patient’s history, clinical picture and laboratory findings, an autoimmune workup was initiated. The laboratory findings on the sixth day after the cesarean section were positive for antinuclear antibodies (ANA) and anti-ds DNA antibodies [1/640 IU/ml (normally negative) and 527 IU/ml (normal values <7 IU/ml), respectively] and low for C3 and C4 complement levels [39 mg/dl (normal values 88–252 mg/dl) and 4 mg/dl (normal values 16–48 mg/dl), respectively] and the patient was diagnosed with SLE. Her proteinuria deteriorated [10,239.6 mg/24 h (normal values <300 mg/24 h)] and it was decided to transfer the patient for further assessment by internal medicine specialists (Table 1).

On admission to the internal medicine clinic of a tertiary university hospital, the patient had a blood pressure of 140/90 mmHg and significant proteinuria [10,000 mg/24 h], with bilateral lower limb and eyelid edema, as well as gradually deteriorating orthopnea. No symptoms such as a butterfly rash or arthritis were present. A chest CT scan showed both subcardiac and pleural effusions. The transthoracic color echo-cardiogram revealed a low ejection fraction of the left ventricle, of ~11%. These findings were consistent with pericardial disease. A multidisciplinary team consisting of a rheumatologist, a nephrologist and an internal medicine physician undertook the care of the patient and decided to transfer her to the high dependency unit (HDU) for close monitoring, where she stayed for two weeks. During her stay at the HDU and five weeks after her admission to the internal medicine clinic, the patient underwent a renal biopsy. The histopathologic report stated that the majority of the glomeruli showed mesangial and endothelial proliferation affecting the entire glomerulus, thus leading to diffuse hypercellularity of the glomeruli, which confirmed the diagnosis of type IV SLE.

Immediately after obtaining these biopsy histology results, which were consistent with diffuse proliferative lupus nephritis, a regimen of immunosuppressants (cyclophosphamide and azathioprine), antihypertensives (ramipril, hydrochlorothiazide, metoprolol and furosemide), glucocorticoids (methylprednisolone) and bisphosphonates (risedronic acid) was initiated. The patient showed gradual clinical improvement and she was discharged from the hospital after twenty days with an ejection fraction of 49% and an arterial blood pressure of 120/80 mmHg.

### 3. Discussion

Systemic lupus erythematosus affects women of reproductive age 15 times more frequently than men and manifests with a wide spectrum of symptoms, signs and laboratory findings, such as rash, arthritis, anemia, thrombocytopenia, serositis, nephritis and/or psychosis [8,9]. Pregnant women with SLE carry a higher risk of preeclampsia and eclampsia. Among women with nephritis, the incidence of preeclampsia and eclampsia may reach 66%. Uterine doppler studies are able to identify pregnancies with high uterine artery pressures, which can indicate early placental changes that lead to preeclampsia [10]. Hypertension, proteinuria and a decline in renal function can be seen in both preeclampsia and lupus nephritis. Differentiating these two conditions can be difficult as they can conditions can also coexist. Lupus nephritis can be confirmed by the presence of decreasing complement levels and increasing double-stranded DNA (dsDNA) antibody levels, in addition to new-onset hypertension and proteinuria [6,7]. Moreover, abnormally low levels of complement and active urine sediment are indicative of lupus nephritis, whilst high serum levels of uric acid and low urine levels of calcium are more typical of preeclampsia. It is essential to accurately determine whether symptoms are due to preeclampsia or to lupus, given the different treatments required [10]. The discrimination between preeclampsia and SLE nephritis can be aided by the ratio of the soluble fms-like tyrosine kinase 1 (sFlt-1) to the placental growth factor (PIGF). This ratio is increased in pregnancy before the onset of preeclampsia. An elevated ratio has a high positive predictive value for preeclampsia, whereas the diagnosis of preeclampsia can be excluded within a week for low ratios [11].

Pregnant women with SLE have fewer CD4+ /CD25+ regulatory T cells, which are also functionally defective. A healthy pregnancy is characterized by a shift from a Th1 cell-mediated to a Th2 antibody-mediated immune response, which is commonly referred to as Th2 polarization. This relative suppression of Th1 cell-mediated immunity underpins the maternal immune tolerance of the fetus. In the setting of Th2 polarization, Th2-mediated diseases, like SLE, may worsen during pregnancy. Common risk factors for disease flares include active disease within six months before conception, a history of multiple flares and discontinuation of hydroxychloroquine. Flares can not only occur at

### Table 1
Course of kidney function.

| Cesarean Section | Day | 1st post-op day | 2nd post-op day | 3rd post-op day | 4th post-op day | 6th post-op day | 7th post-op day | 10th post-op day |
|-----------------|-----|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Urea            | 61.9 mg/dl | 67.2 mg/dl | 82.2 mg/dl | 76.6 mg/dl | 83.5 mg/dl | 99.4 mg/dl | 104.9 mg/dl | 112.6 mg/dl |
| Creatinine      | 1.3 mg/dl  | 1.6 mg/dl  | 1.7 mg/dl  | 1.2 mg/dl  | 1.2 mg/dl  | 1.4 mg/dl  | 1.6 mg/dl  | 10.239.6 mg/24 h |
| 24-h urine protein | N/A | 2134 mg/24 h | N/A | N/A | N/A | N/A | N/A | N/A |
any gestational age, but also in the postpartum period, as in the above case. Active lupus nephritis associated with a lupus flare increases the risk of maternal and neonatal morbidity and is associated with a higher risk of hypertension in pregnancy. Furthermore, a history of nephritis and active nephritis carry greater risks for hypertension and preeclampsia compared with women with SLE without a history of lupus nephritis. Progressive renal impairment may occur. It is generally mild and the need for dialysis is rare, even in women with active lupus nephritis. The risk of severe morbidity, including eclampsia, stroke and maternal death, approaches 1%. Consequently, close monitoring with monthly assessments of disease activity is recommended [12].

SLE does usually not impede fertility in women [10], except for those with antiphospholipid syndrome (APS), advanced renal insufficiency [i.e. creatinine ≥3 mg/dl (normal values 0.6–1.4 mg/dl)] or those previously treated with cytotoxic alkylating agents [12]. In order to minimize complications of future pregnancies in women with SLE, administration of low-dose aspirin is recommended, starting before 16 weeks of gestation and continuing throughout pregnancy. Women with SLE and APS should continue aspirin treatment for prophylaxis against preeclampsia and should heparin or low-molecular-weight heparin (LMWH) should be added [10].

Medications considered as safe throughout all trimesters of pregnancy and during lactation to prevent and treat lupus flares are hydroxychloroquine, azathioprine, cyclosporine and tacrolimus. Corticosteroids are safe to use to control symptoms; acetylsalicylic acid are also safe. Methotrexate, mycophenolate mofetil and cyclophosphamide must be stopped before pregnancy due to proven teratogenicity and should be avoided during breastfeeding. Along with the above, antihypertensive drugs for preexisting or pregnancy-induced hypertension/preeclampsia include methyldopa, nifedipine and/or labetalol as safe first-line treatment options (single or combined) at any stage of conception, pregnancy or lactation. Second-line medication during pregnancy includes hydralazine or doxazosin. It should be emphasized that angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers should be discontinued before conception, because they are associated with an increased risk of congenital abnormalities [9].

The timing and mode of delivery should be discussed among obstetricians, rheumatologists, nephrologists and neonatologists experienced in the management of labor in the setting of renal disease, especially when a patient is about to deliver before 37 weeks of gestation. Moreover, if the woman is breastfeeding, considerations should be given to the safety of immunosuppressive drugs for the infant [12].

In summary, care for pregnant women with SLE should be coordinated by obstetricians, rheumatologists, nephrologists and midwives specialized in high-risk pregnancies. Timely treatment of flares is vital for the optimization of perinatal outcomes and women should not discontinue antirheumatic drugs compatible with pregnancy [9]. Pregnant patients are more prone to renal involvement [13]. Flares can also occur in the puerperium. As a result, a high grade of clinical suspicion and, most importantly, constant watchfulness and rapid interventions – if necessary by a multidisciplinary team – are required to avoid the detrimental effects of lupus nephritis in these women and minimize the burden of nephrotic syndrome postpartum.

Contributors
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Conflict of interest
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Patient consent
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