Steroid-induced psychosis in the context of lupus podocytopathy: a rare and challenging case

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ABSTRACT

Background: Lupus podocytopathy (LP) is a rare histopathological diagnosis of renal biopsies performed in the context of systemic lupus erythematosus (SLE) with renal involvement. Steroid-induced psychosis is a well-documented phenomenon.

Case Presentation: A 55-year-old woman, diagnosed with SLE, went to the emergency department due to asthenia, inflammatory polyarthritis, and decreased urinary output. The blood panel showed hypoalbuminemia and acute kidney injury and the protein/creatinine ratio was elevated. She was admitted with a diagnosis of probable lupus nephritis (LN) and pulses of methylprednisolone were started. During hospitalization, an amplified study was conducted. A 24-hour urine sample showed proteinuria in the nephrotic range. Renal biopsy was conducted and the results showed aspects suggestive of class II lupus nephropathy and the suspicion of LP was therefore high. Despite favorable evolution with high-dose corticosteroid oral therapy, the patient began to experience behavioral changes with delusional and persecutory thoughts, compatible with psychosis, which led to the introduction of tacrolimus and the rapid reduction in steroid doses. During follow-up consultation, the diagnosis of podocytopathy was confirmed by electron microscopic evaluation, with a diffuse fusion of the podocyte pedicels and without subepithelial deposits or organized structures.

Conclusion: LP is a rare histopathological diagnosis and should be suspected in cases of LN with nephrotic proteinuria. Kidney biopsy and electron microscopy are essential in confirming the diagnosis. It is mandatory to recognize and manage steroid-induced psychosis during high-dose corticosteroid therapy. The use of tacrolimus is an important alternative treatment option in such cases.

Keywords: Podocytopathy, systemic lupus erythematosus, tacrolimus, internal medicine.

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Background

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with variable clinical and pathological presentation. However, renal involvement in patients with SLE is common (30% to 90% of patients) and can lead to high morbidity and mortality [1].

Interpretation of renal biopsies from patients with SLE is complicated due to a large range of morphological variability of the lesions. Renal involvement by SLE can simulate the pattern of any primary glomerulonephritis. Furthermore, injuries can be different in terms of morphological characteristics and distribution between patients, between glomeruli within a sample, or even within a given glomerulus [2, 3].

In SLE, nephrotic-range proteinuria typically signals the presence of proliferative lupus nephritis (LN) (class III/IV) and/or membranous LN (class V, with or without concomitant class III or IV lesions). However, in rare instances, SLE patients with nephrotic syndrome have kidney biopsy findings of normal glomeruli or focal segmental glomerulosclerosis (FSGS) lesions, with or without mesangial proliferation, on light microscopy; the absence of subepithelial or subendothelial deposits on immunofluorescence and electron microscopy; and diffuse foot process effacement on electron microscopy. This pattern, termed lupus podocytopathy (LP), is a unique form of LN that mimics minimal change disease (MCD) or primary FSGS and represents approximately 1% of LN biopsies [4].

Steroid-induced psychosis is a well-documented phenomenon. It usually occurs with oral systemic steroid treatment and is more common at higher doses [5]. In such cases, increased corticosteroid doses lead to mental

health changes, including depressive and/or psychotic symptoms. These two conditions, while overlapping in presentation, have distinct underlying mechanisms that influence their management, as well as treatment strategies. Differentiation is critical.

This paper explores a clinical case of steroid-induced psychosis in a patient with SLE, highlighting the nuances of diagnosis and the interplay between treatment and neuropsychiatric complications.

Case Presentation

A 55-year-old Afro-American woman, born in Brazil and living in Portugal for 30 years, was diagnosed at age 17 with SLE. She reported mucocutaneous and joint involvement of lupus, at the time. Her usual medication was hydroxychloroquine 400 mg on alternate days and prednisolone (PDN) 5 mg/day. She was in remission for several years and did not have any other organ involvement in the disease.

She was admitted to the emergency department due to inflammatory polyarthralgias and edema of the proximal interphalangeal joints of the hands, knees, and ankles bilaterally, which began one week prior. She also noted a decrease in her urinary output. Her vital signs were: blood pressure of 157/110 mmHg, heart rate of 78 bpm, oxygen saturation of 100% on room air, and no fever. Physical examination highlighted bilateral edema of the lower limbs and no signs of arthritis. A blood and urine analysis was performed (Table 1).

Due to the presumption of LN (hypertension, edema, acute kidney injury, hypoalbuminemia, and high protein levels in the urine sample), she was admitted to the Internal Medicine department. She was given 3 pulses of methylprednisolone 500 mg/day and then started on oral PDN 1 mg/kg/day (60 mg).

During the hospital stay, a thorough study was completed, as shown in Tables 2–4:

In this case, the patient's manifestations were consistent with nephrotic syndrome, including proteinuria above 3,5 g in a 24-hour urine sample, dyslipidemia, hypoalbuminemia, and edema. So further investigation with a kidney biopsy evaluation was important to exclude other coexisting glomerular pathologies. The nephrotic syndrome differential diagnosis included coexisting primary glomerular diseases such as MCD or FSGS, as these may occur independently in lupus patients. Secondary causes, such as drug-induced glomerulopathies, diabetic nephropathy, or amyloidosis, should also be excluded.

A kidney biopsy is essential in the diagnosis of LN. The result was a class II LN with low levels of immune

Table 1. *Blood and urine analysis in the emergeny department.*

Hemoglobin	14.3 g/dl (11.9-15.6 g/dl)	Urea	96 mg/dl (19-49 mg/dl)
Hematocrit	41.40% (36.6%-45%)	Creatinine	1.5 mg/dl (baseline 0.9 mg/dl)
MGV	85.9 fl (82.9-98 fl)	Potassium	5.5 mmol/l (3.5-5.1 mmol/l)
MGH	29.7 pg (27-32.3 pg)	Sodium	133 mmol/l (136-145 mmol/l)
Leukocytes	7.3 10*3/ul (4-11 10*3/Ul)	Chloride	104 mmol/l (98-107 mmol/l)
Neutrophils	4.6 10*3/ul (1.8-7.1 10*3/Ul)	Calcium	9.0 mg/dl (8.3-10.6) (corrected by Albumin)
Lymphocytes	1.9 10*3/ul (1.2-3.4 10*3/ul)	Albumin	2.0 g/dl (3.4-5 g/dl)
Platelets	294,000/ul (150,000–400,000/ul)	Total protein	5.3 g/dl (5.7-8.2 mg/dl)
Creatinine in spot urine	81.7 mg/dl (15-278 mg/dl)	Leukocytes in spot urine	Negative
Protein in spot urine	572.1 mg/dl (1-14 mg/dl)	Erythrocytes in spot urine	Positive
Ratio Protein/creatine in spot urine	7.0 mg/mg (<0.2 mg/mg)	Protein in spot urine	Positive

Table 2. *Renal, adrenal, and bladder ultrasound.*

RENAL, ADRENAL AND BLADDER ULTRASOUND	The kidneys have regular contours, normal morphology and normal dimensions. The parenchymal thickness appears to be preserved bilaterally, admitting a slight loss of parenchymal-sinus differentiation due to increased cortical echogenicity. There are no pyelocaliceal ectasias nor images that suggest with unequivocal certainty the presence of a lithiasis focus. No fluid or perirenal collections. Bladder without parenchymal changes

Table 3. *Complete study for nephrotic syndrome manifestations and serum antibody results.*

Triglycerides	369 mg/dl (<150 mg/dl)	Protein in 24 hour-urine sample	7.2 g/24 hour	Ds-DNA	+
Total cholesterol	589 mg/dl (<200 mg/dl)			ANA	+ (1/320)
Cholesterol - HDL	83 mg/dl (>45 mg/dl)			RNP	+
Cholesterol - LDL	460 mg/dl (<130 mg/dl)			Smith (+specific)	+

Table 4. *Kidney biopsy results.*

Kidney biopsy (Figure 1 in PAS staining and Figure 2 in trichrome staining)	Class II LN with mesangial proliferation and presence of scarce intramembranous and even subepithelial immunocomplex IgG deposits in peripheral capillary loops

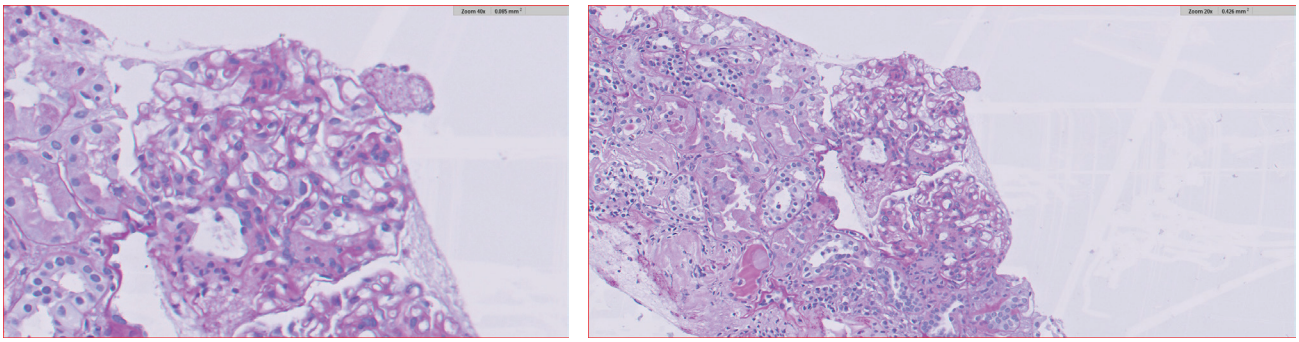

Figure 1. *Different glomeruli with mesangial hypercellularity with PAS staining - it highlights the minimal involvement of glomerular capillaries and absence of proliferative changes typically seen in more severe forms of LN, supporting the rare diagnosis of LP.*

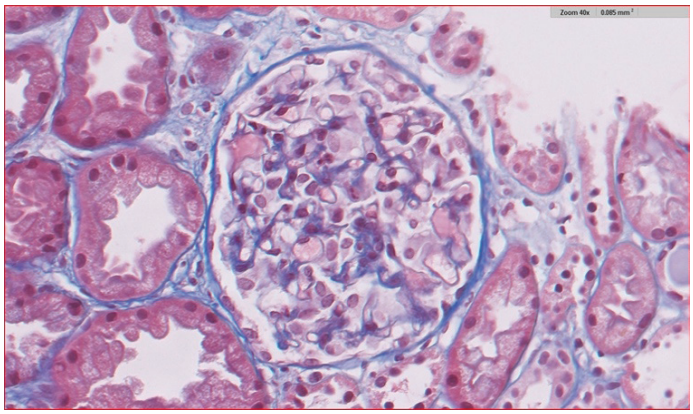

Figure 2. *Trichrome staining showing the absence of significant fibrosis or sclerotic changes, reinforcing that the renal damage is primarily due to podocyte injury rather than chronic structural damage. This underscores the reversibility of the condition with appropriate treatment.*

complexes deposited within the mesangium (Figure 1 in PAS staining and Figure 2 in trichrome staining). Usually, these patients have mild renal manifestations, presenting with hematuria and/or proteinuria. In class I and II LN, the treatment guidelines focus on blood pressure control (preferably through the blockade of the renin-angiotensin-aldosterone system), cardiovascular risk management, and the use of antimalarials such as hydroxychloroquine [2].

However, in this case, the combination of nephrotic syndrome and the kidney biopsy findings of class II LN led us to dig deeper. The presence of marked nephrotic range proteinuria (7.2 g/24 hour) and hypoalbuminemia suggested that another glomerular condition might be at play. This raised the possibility of LP, a rare subtype of LN marked by diffuse podocyte damage and effacement. The absence of significant subepithelial or subendothelial immune complex deposits, along with the mesangial proliferation seen on light microscopy, strengthened this suspicion, showing how essential the kidney biopsy was essential to help with the diagnosis. Confirmation required electron microscopy, which revealed extensive podocyte effacement - a hallmark feature of LP.

Despite a favorable clinical evolution with the introduction of high-dose corticosteroid therapy, on the tenth day, the patient began to experience behavioral changes with delusional and persecutory thoughts. A magnetic resonance image of the brain was performed and there were no pathological changes. After a psychiatry consultation, she was diagnosed with steroid-induced psychosis. She needed to start olanzapine, among others, to control the psychotic symptoms.

The hypothesis of neuropsychiatric involvement of SLE was unlikely, given the onset of psychotic symptoms only after the introduction of steroid therapy and simultaneous improvement of the nephrotic syndrome. Thus, considering the diagnosis of induced psychosis, the need for rapid weaning from steroid therapy, and the presumptive diagnosis of LP, it was decided to start tacrolimus.

Tacrolimus, a calcineurin inhibitor, reduces intraglomerular cell proliferation and stabilizes podocytes by preserving the actin cytoskeleton, which is disrupted in

podocyte injury. This dual action helps restore the filtration barrier, reducing proteinuria and normalizing podocyte function. Its effectiveness as both an immunosuppressant and podocyte stabilizer makes it a valuable option, especially when steroid-related adverse effects limit treatment [3]. Tacrolimus was started at 3 mg/day, allowing rapid reduction of corticosteroids. The psychosis gradually improved and resolved over a few days with weaning from steroid therapy.

Discussion

LP is a rare condition, identified in only 1% of kidney biopsies performed in the context of LN. It´s characterized by the widespread fusion of podocyte pedicels and the absence of immune complex deposits at subendothelial and subepithelial on electron microscopy. These features make it crucial to differentiate LP from primary podocyte diseases like MCD or FSGS. While the exact mechanisms remain unclear, they may involve disruption of the podocyte cytoskeleton. Diagnosis relies on the clinical presentation, lupus-specific markers, and ruling out typical LP features on histology [4].

In this case, the presence of nephrotic syndrome alongside kidney biopsy findings of class II LN prompted further investigation. Class II LN typically causes mild proteinuria and is not usually associated with nephrotic syndrome. However, the marked proteinuria (7.2 g in a 24-hour urine sample), hypoalbuminemia, and biopsy findings of mesangial proliferation on light microscopy suggested an alternative diagnosis. Electron microscopy of the kidney biopsy was essential to confirm the diagnosis, revealing the absence of significant immune complex deposits. Taken together, these findings led to the diagnosis of LP [4].

This case also highlighted the challenge of managing neuropsychiatric complications during treatment. Steroid-induced psychosis, a known side effect of high-dose corticosteroid therapy, affects up to 10% of patients. In this case, the patient developed delusional and persecutory thoughts, which required immediate psychiatric evaluation. Differentiating between steroid-induced psychosis and lupus psychosis is essential and can change the course of treatment for these patients [5]. This underscores the importance of monitoring for neuropsychiatric side effects in patients on high-dose steroid therapy. Regular mental health assessments and educating patients and caregivers about potential mood or behavioral changes are essential for early detection and intervention, helping to prevent significant complications.

Finally, the therapeutic value of tacrolimus in this case deserves attention. Tacrolimus serves as both an immunosuppressant and a podocyte stabilizer, reducing glomerular cell proliferation and preserving the podocyte cytoskeleton. In this patient, tacrolimus played a key role in managing LP while facilitating a fast corticosteroid taper [3].

Conclusion

During follow-up consultation, the diagnosis of LP was confirmed by electron microscopy showing diffuse fusion of the podocyte pedicels, without subepithelial deposits or organized structures present.

Currently, 9 months after discharge, with tacrolimus 3 mg/day and PDN 2.5 mg/day, the patient is in remission of the disease: she has no systemic or renal symptoms, the renal function is normal, the proteinuria is solved and there are no psychotic symptoms.

This case highlights the importance of a multidisciplinary approach in the management of complicated cases of SLE, especially those with uncommon renal phenotypes and treatment-related complications. Our multidisciplinary team approach by internal medicine, nephrology, and psychiatry, was fundamental to the diagnosis of LP, its differential diagnosis versus other podocyte diseases, and management of corticosteroid-induced psychosis. Clinical monitoring during the course of treatment is essential for early identification of adverse effects like neuropsychiatric symptoms, which require timely intervention. The ability to adapt treatment strategies, including the introduction of tacrolimus and rapid steroid tapering, underlines the value of an integrated approach in ensuring favorable outcomes for both renal and systemic disease management.

Learning Points

- Identify LP as a rare subtype of LN.
- Highlight the critical role of kidney biopsy and electron microscopy in diagnosis.
- Emphasize the significance of promptly identifying and addressing steroid-induced psychosis.
- Recognize tacrolimus as a valuable alternative in managing steroid-related complications.

What is new

This case shows how in every patient we should look at all sides and always look for adverse events during the treatment course. This case is about a lupus-diagnosed patient who presented with a nephrotic syndrome and a biopsy with the result of a Class II LN. The authors believed it was a podocyte disease which was confirmed with electronic microscopic evaluation. Alongside her steroid treatment, she developed psychotic behavior, making them change the treatment.

List of Abbreviations

LP	Lupus podocytopathy
SLE	Systemic lupus erythematosus
LN	Lupus nephritis
FSGS	Focal segmental glomerulosclerosis
MCD	Minimal change disease
PDN	Prednisolone
bpm	Beats for minute
HDL	High Density Lipoprotein
LDL	Low-density lipoprotein
PAS	Periodic acid–Schiff

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Conflicts of interest
The authors declare that they have no conflict of interest regarding the publication of this case report.

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Consent for publication
Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Author contributions
We were all involved in the patient's care and in drafting and writing the manuscript. PPM, MBM, RGP, JA, GT, CR and VG have accessed and verified the data. PPM and VG were responsible for the decision to submit the manuscript for publication.

Data availability statement
The data that support the findings of this case are available from the corresponding author, FSV, upon reasonable request.

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Summary of case

1	Patient (gender, age)	55 years, female
2	Final diagnosis	LP
3	Symptoms	Inflammatory polyarthralgias and edema
4	Medications	Methylprednisolone, PDN, Tacrolimus and Olanzapine
5	Clinical procedure	Renal biopsy
6	Specialty	Internal medicine