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Lupus Podocytopathy: A Rare Cause of Nephrotic Syndrome in Patients with Systemic Lupus Erythematosus

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Abstract

Lupus podocytopathy, a unique form of lupus nephritis, mimics minimal change disease (MCD) or primary focal segmental glomerulosclerosis (FSGS) and represents approximately 1% of lupus nephritis biopsies. Lupus podocytopathy is characterized by diffuse epithelial cell foot process effacement without immune complex deposition or with only mesangial immune complex deposition. We present the case of a young woman with systemic lupus erythematosus (SLE) who presented with nephrotic syndrome and acute kidney injury (AKI) and was subsequently diagnosed with lupus podocytopathy.

Keywords: Lupus podocytopathy, Nephrotic syndrome, SLE, Lupus nephritis, Minimal change disease

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that may affect any organ in the body and is associated with a wide range of clinical and immunologic manifestations, of which lupus nephritis is the major cause of morbidity and mortality. It affects around 40% of SLE patients throughout the course of their lives.¹ Lupus nephritis is characterized by the formation of autoantibodies against a wide variety of autoantigens, particularly against chromatin material like double-stranded (ds) DNA and nucleosomes, which happens as a result of defective clearance of apoptotic material, and necrotic cells.² The pathogenesis of lupus nephritis is complicated and involves different mechanisms. It is primarily caused by the immune complex deposition and complement activation, which induce tissue inflammation and glomerular damage. Interferon alpha and other inflammatory mediators are released as a result of abnormal adaptive and innate immune responses, amplifying glomerular lesions.^{3,4}

There are different subtypes of lupus nephritis. Lupus podocytopathy, is a unique form of lupus nephritis, which mimics minimal change disease (MCD) or primary focal segmental glomerulosclerosis (FSGS) and represents approximately 1% of lupus nephritis biopsies.⁵ Lupus podocytopathy is defined by diffuse epithelial cell foot process effacement without immune complex deposition or with only mesangial immune complex deposition visualized on electron microscopy.⁶ We present the case of a young woman with systemic lupus erythematosus (SLE) who presented with nephrotic syndrome and acute kidney injury (AKI).

2. Case presentation

A 25-year-old woman with past medical history of SLE presented to the emergency department complaining of generalized swelling for 2–3 weeks, predominantly in the legs. The patient also complained of a productive cough but denied any dyspnea. Patient was diagnosed with SLE six months ago when she was admitted at another

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hospital with AKI. She was discharged on steroids, but she was not compliant with her medications. On initial examination, vital signs were within normal limits, lung auscultation revealed bilateral rales, and the lower extremities had 3+ pitting edema bilaterally. Significant labs on admission showed creatinine of 2.7 mg/dL (her baseline creatinine is within normal range), BUN of 68 mg/dL, and a serum albumin of less than 1.5 g/dL. Initial urinalysis showed protein >1000 mg/dL along with red blood cell (RBC) greater than 50 HPF. The initial urine protein creatinine ratio (UPCR) was 23.89. Total cholesterol was elevated to 700 mg/dL. Erythrocyte sedimentation rate was elevated to 78 mm/h but double stranded DNA antibody, C3, C4, and C-reactive protein were normal. A kidney biopsy was performed due to the presence of proteinuria and high suspicion of lupus nephritis, which showed “diffuse podocytopathy without immune deposits mimicking minimal change disease (less evidence of FSGS). Acute tubular injury with epithelial cell necrosis and associated mild interstitial inflammation.” (Fig. 1) On the immunofluorescence, neither global sclerosis nor significant immune deposits were seen in the glomeruli. Rheumatology and nephrology were consulted, and the patient was treated with steroids, mycophenolate mofetil, hydroxychloroquine, and rituximab. At discharge, serum creatinine returned to baseline (after reaching a peak of 4), serum albumin increased to 3 g/dL, and UPCR decreased to 2.34. At one month follow up in the clinic, the patient's lower extremity edema had resolved and creatinine and UPCR were in normal range.

3. Discussion

A classification system was established by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) in 2004 to improve reproducibility, diagnosis, and treatment of lupus nephritis based on the underlying glomerular lesions.⁷ The Location of immune-complex (IC) deposits and the presence of glomerular proliferative lesions (mesangial, endocapillary, and extra capillary proliferation) are the main criteria used to categorize LN. The ISN classification is shown in the table below.

The revised 2018 version of the ISN and RPS classification of LN does not yet include the entity known as LP. In SLE patients, nephrotic syndrome most commonly appears as proliferative lupus nephritis (class III, class IV) or membranous lupus nephritis (class V).^{7,8} However, in rare instances, nephrotic syndrome may appear as lupus

Classification of lupus nephritis using the ISN/RPS 2004 classification.

Class	Definition
I	Minimal mesangial LN
II	Mesangial proliferative LN
III	Focal lupus nephritis (<50% of glomeruli)
	III (A): purely active lesions: focal proliferative LN
	III (A/C): active and chronic lesions: focal proliferative and sclerosing LN
	III (C): chronic inactive with glomerular scars: focal sclerosing LN
IV	Diffuse LN (\geq 50% of glomeruli), Segmental (IV-S) or global (IV-G) lupus nephritis
	IV-S (A) or IV-G (A): purely active lesions: diffuse segmental or global proliferative LN
	IV-S (A/C) or IV-G (A/C): active and chronic lesions: diffuse segmental or global proliferative and sclerosing LN
	IV-S (C) or IV-G (C): inactive with glomerular scars: diffuse segmental or global sclerosing LN
V	Membranous LN
VI	Advanced sclerosing LN (\geq 90% globally sclerosed glomeruli without residual activity)

ISN: International Society of Nephrology, RPS: Renal Pathology Society.

podocytopathy, a glomerular lesion mimicking minimal change disease or focal segmental glomerulosclerosis. kidney biopsy of these patients shows normal glomeruli or (FSGS) lesions with or without mesangial proliferative features and no endocapillary proliferation/inflammation on LM, (unlike Class III and IV LN), and no glomerular capillary immune deposits on IF (unlike Class V LN). The presence of diffuse FPE on electron microscopy confirms the diagnosis of lupus podocytopathy.^{6,9,10}

Patients with LP can have different morphologic findings of their kidneys, and subsequently can be divided into three subgroups based on their histological findings: those with normal light microscopy findings without mesangial proliferation defined as MCD; those with biopsy findings as FSGS; and the third group classified as mesangial proliferative LN (class I or II LN with concomitant podocytopathy).⁹ Full nephrotic syndrome is the major clinical feature of LP as seen in our case, and presents in all three subgroups with no significant differences. Acute kidney injury, another clinical manifestation may occur uncommonly in LP patients. A cohort study in 2016 which was performed on 50 LP patients, showed that AKI and severe tubule–interstitial injury was significantly higher among patients with FSGS subtype, and they had much lower remission rate.⁵

Previously reported cases of lupus podocytopathy have shown positive serology, in particular ANA and anti-ds-DNA, associated with it.^{11,12} But there are cases in which anti-dsDNA on time of

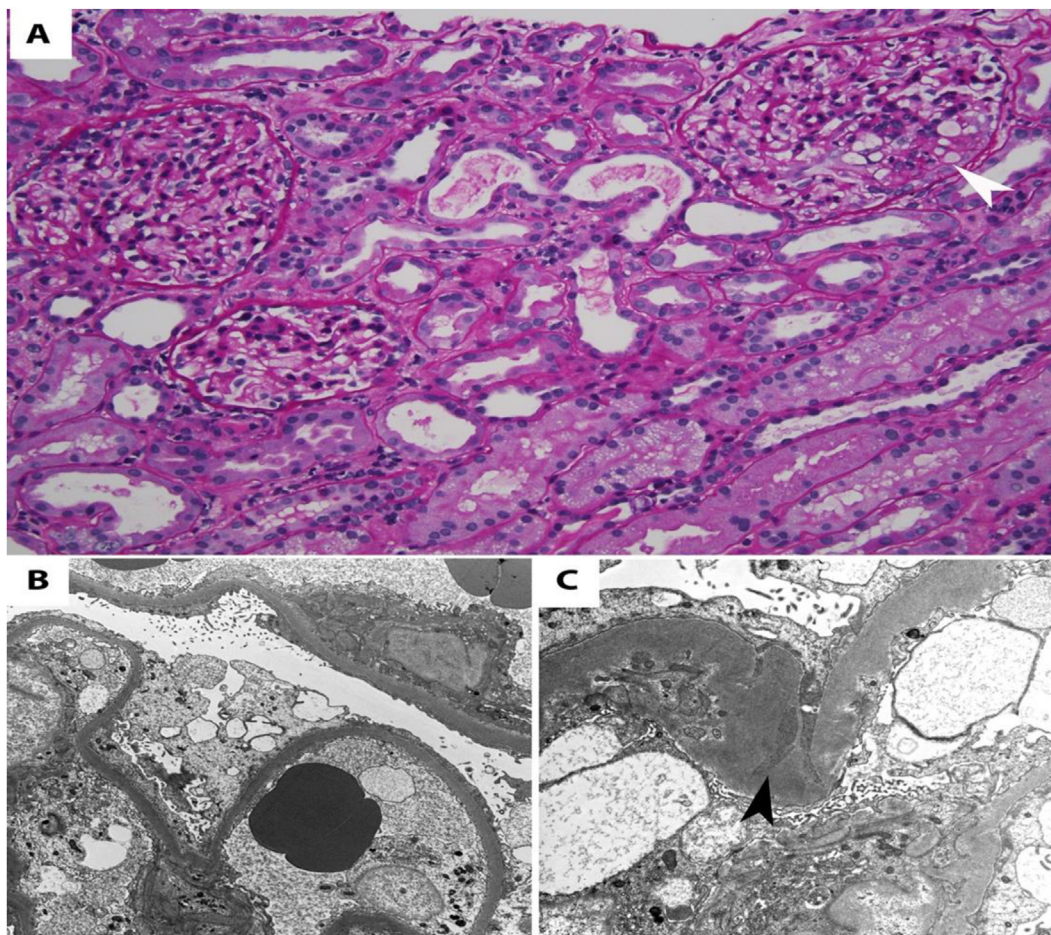


Fig. 1. A- H&E stain that shows 2 normal glomeruli on the left without mesangial proliferation. The white arrowhead on the right of the figure points to rare segmental sclerosis; B-electron microscopy showing normal basement membrane without subepithelial or subendothelial deposits; C- higher power electron microscopy figure that points to an area of podocyte foot process effacement (black arrowhead, you can no longer see the individual foot processes that extend into the glomerular basement membrane).

presentation has been negative.^{13,14} Even though our patient's serological markers for SLE were positive six months ago, her markers on presentation this time were not strongly positive. This discrepancy does raise the possibility that lupus podocytopathy might not be a manifestation of SLE flare. However, more data is needed to make such assumption.

Glucocorticoids are the first line therapy in management of LP, and most of the patients respond well to them.¹⁵ However, the FSGS forms have a lower rate of complete remission compared to MCD and mesangial proliferative cases. Approximately 50 percent of patients with LP experience relapses of the kidney disease.^{5,6} Additional immunosuppressive medications such as mycophenolate mofetil, calcineurin inhibitors (CNIs), cyclophosphamide, and rituximab may be required to help decrease the rate of relapse in patient with LP.⁹ A study done by Hu WX, Chen YH, Bao H et al., in 2015 supported

this recommendation, and showed that glucocorticoids in conjunction with other immunosuppressive agents, significantly reduced the rate of relapse by more than 50%.¹⁵ Given that FSGS lupus podocytopathy patients tend to have more severe forms of renal involvement and have less respond rate to glucocorticoids alone; this combination therapy would also be beneficial for them in terms of increasing the remission rate. Among steroid-sparing agents CNIs have shown higher remission rates and has been more advantageous for long-term renal outcomes in LNs with severe podocyte effacement.¹⁶ Tacrolimus, a CNIs has been reportedly effective in reducing proteinuria in patients with lupus nephritis.^{17,18}

There is a novel calcineurin inhibitor under the name of voclosporin was approved in 2021 by FDA for treatment of patients with LN. A randomized phase 3 trial done in 2021 showed that voclosporin in combination with Mycophenolate mofetil (MMF)

and low-dose steroids had clinically and statistically better renal response rate than MMF and low-dose steroids alone.¹⁹ However, studies for treatment of lupus podocytopathy are limited and the managements is mostly based on observational studies. Therefore more trials are required to assess the efficacy of different treatment options in conjunction with steroids.

Conflict of interest

There is no conflict of interest.

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