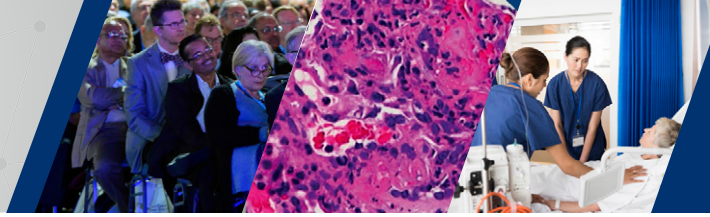

A Pregnant Woman with Lupus and Nephrotic-Range Proteinuria

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Introduction

For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are one of the most exciting venues. The Nephrology Quiz and Questionnaire (NQQ) is the essence of clinical nephrology and represents what drew all of us into the field of nephrology. This year's NQQ in surprisingly temperate Chicago, with full-house attendance, was no exception. The expert discussants prepared vignettes of puzzling patients, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of key clinical areas of nephrology. These eight interesting patients were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her case discussions, which serves as the text of this article (Mark A. Perazella and Michael Choi, comoderators).

Patient 1

A 20-year-old woman in the first trimester of pregnancy presents to her rheumatologist with concern about a flare of lupus, which had been diagnosed 6 years earlier. To this point, she has only had arthralgias managed on hydroxychloroquine 200 mg daily, but now she reports subjective fevers along with worsening joint pains in her elbows, wrists, and knees. On the rheumatologist's examination, she has a BP of 99/59 mmHg with no rash, no joint effusions, and trace lower extremity edema. Laboratory values from the rheumatologist's office reveal serum creatinine 0.7 mg/dl, serum albumin 2.5 g/dl, 3+ protein and 3+ blood on urinalysis, and urine protein-to-creatinine ratio of 3.5 g/g. Both antinuclear antibody and antidouble-stranded DNA are positive. Serum levels of C3 and C4 are both decreased.

She is referred to a nephrologist for consultation.

Question 1

What would you recommend for this patient?

A. Renal biopsy
B. Referral to obstetrician to discuss elective termination given likelihood of preeclampsia
C. Empirical therapy with steroids and mycophenolate mofetil
D. Empirical therapy with steroids and azathioprine
E. Increase dose of hydroxychloroquine to 200 mg twice a day

Discussion of Question 1

A renal biopsy is indicated to confirm the diagnosis of lupus nephritis, determine the class of nephritis, and, ultimately, guide treatment decisions (answer A is correct) (1,2). This woman presents with nephrotic-range proteinuria, hypoalbuminemia, microscopic hematuria, and active lupus serologies suggestive of lupus nephritis, but her presentation can be seen across a spectrum of lupus nephritis lesions (Table 1). Preeclampsia is unlikely to present this early in pregnancy, and there is no evidence of hypertension, a requirement for the diagnosis of preeclampsia (3). Empirical therapy with immunosuppression for lupus nephritis is not recommended when a biopsy can be obtained. Indeed, the clinical and laboratory presentation of this patient could be associated with classes II, III, IV, and/or V lupus nephritis, each with its own distinct treatment. Increasing the dose of hydroxychloroquine would not be appropriate management, because this drug is not considered an effective therapy for active lupus nephritis and is used, instead, for management of extrarenal symptoms and prevention of lupus flares (4).

Renal biopsy in this patient should, therefore, be pursued. Although the patient is pregnant, a biopsy procedure this early in the pregnancy carries the same safety profile as a biopsy in a nonpregnant patient. In a systematic review of 39 studies on kidney biopsies in pregnant patients encompassing 243 biopsies during pregnancy compared with a control group of 1236 postdelivery biopsies, only four patients with major bleeding complications were reported, all occurring after biopsies performed at 23–26 weeks of gestation (5). Approximately 7% of all women who underwent biopsies during pregnancy experienced some complication; although most of these cases were deemed minor (*e.g.*, small hematomas that did not require a transfusion and gross hematuria of several hours in duration with strong loin pain), this complication rate was significantly higher than reported in postpartum biopsies and biopsies of nonpregnant individuals (6). Notably, kidney biopsies performed for suspected diagnoses of glomerular disease or preeclampsia led to therapeutic changes in 66% of patients (5).

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Table 1. The classification of lupus nephritis, including lupus podocytopathy, with associated clinical presentation

Class	Biopsy Findings	Clinical Features	Patients Presenting with Nephrotic Syndrome, %
Class I: minimal mesangial LN	No LM abnormalities; isolated mesangial IC deposits on IF and/or EM	Normal urine or microscopic hematuria	0
Class II: mesangial proliferative LN	Mesangial hypercellularity or matrix expansion with mesangial IC deposits on IF and/or EM	Microscopic hematuria and/or low-grade proteinuria	0
Lupus podocytopathy	Normal glomeruli, FSGS, or mesangial proliferation on LM; IC deposits absent or limited to mesangium on IF and/or EM; diffuse and severe foot process effacement on EM	Nephrotic syndrome	>90
Class III: focal LN	<50% of Glomeruli on LM display segmental (<50% of glomerular tuft) or global (>50% of glomerular tuft) endocapillary and/or extracapillary proliferation or sclerosis; mesangial and focal subendothelial IC deposits on IF and EM	Nephritic urine sediment and subnephrotic proteinuria	30
Class IV: diffuse LN	≥50% of glomeruli on LM display endocapillary and/or extracapillary proliferation or sclerosis; mesangial and diffuse subendothelial IC deposits on IF and EM	Nephritic and nephrotic syndromes, hypertension, reduced kidney function	50
Class V: membranous LN[a]	Diffuse thickening of the glomerular capillary walls on LM with subepithelial IC deposits on IF and EM with or without mesangial IC deposits	Nephrotic syndrome	80
Class VI: advanced sclerosing LN	>90% of Glomeruli on LM are globally sclerosed with no residual activity	Advanced CKD	<10

Lupus podocytopathy, listed separately here, is not a distinct classification according to the International Society of Nephrology/Renal Pathology Society classification but rather, a concomitant diagnosis made alongside class I or class II LN. LN, lupus nephritis; LM, light microscopy; IC, immune complex; IF, immunofluorescence; EM, electron microscopy.
[a]Class V may coexist with class III or IV, in which case both classes are diagnosed.

In this patient presentation, a renal biopsy is performed and shows a mesangial proliferative lupus nephritis (class II) with widespread complete foot process effacement (Figure 1), consistent with a diagnosis of lupus podocytopathy.

Question 2

On the basis of the renal biopsy findings, what would you recommend for this patient?

A. Labetalol 200 mg twice daily during pregnancy and then change to angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) after delivery
B. No therapy until after delivery and then start ACE inhibitor or ARB
C. Tacrolimus initiated at 0.1 mg/kg per day in divided doses with titration to trough level of 5–10 ng/ml
D. Prednisone 60 mg daily until remission of proteinuria (maximum of 12 weeks) and then taper
E. Prednisone 60 mg daily until remission of proteinuria (maximum of 12 weeks), taper, and azathioprine 1.5 mg/kg per day during pregnancy

Discussion of Question 2

This patient should be treated with prednisone (high dose) until remission of proteinuria followed by a taper, akin to the treatment of minimal change disease (MCD) or FSGS (answer D is correct). Lupus podocytopathy is an unusual variant of lupus nephritis, presenting as nephrotic syndrome with diffuse foot process effacement in the

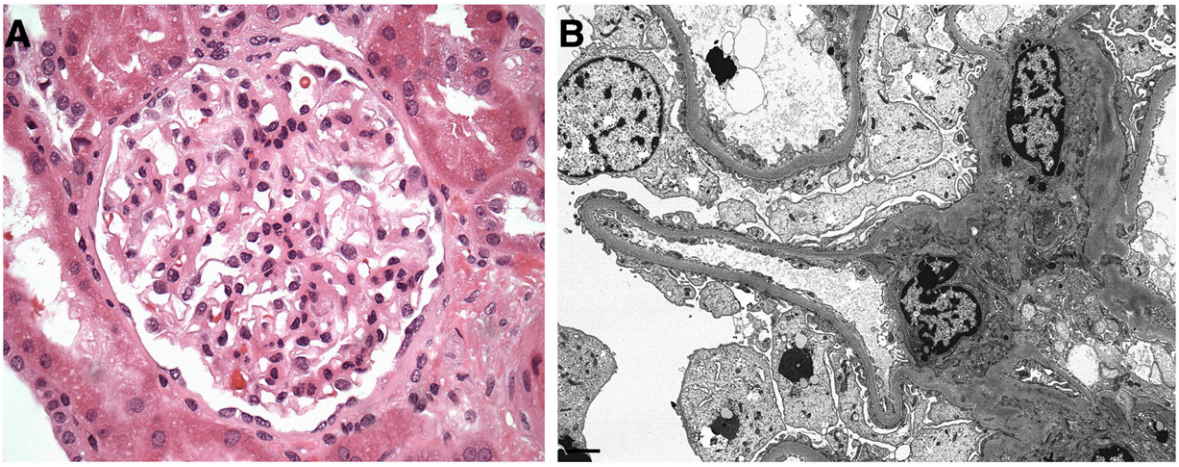

Figure 1. | Kidney biopsy of patient in case discussion is consistent with a diagnosis of lupus podocytopathy. (A) Light microscopy reveals a mesangial proliferative GN. Immunofluorescence microscopy, not shown, reveals granular global mesangial deposits that stain positive for IgG, IgM, IgA, C3, and C1q (full house pattern). Original magnification, ×400. (B) Electron microscopy shows rare mesangial deposits and complete foot process effacement. The final histopathology diagnosis is a class II lupus nephritis with superimposed lupus podocytopathy. Original magnification, ×8000. Courtesy of Glen Markowitz (Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, New York, NY).

absence of peripheral capillary wall immune deposits (Table 1). As with other forms of lupus nephritis, patients with lupus podocytopathy typically present with (+) antinuclear antibody and antidouble-stranded DNA testing, and depressed complement levels (C3 and/or C4) have been reported in up to two thirds of patients (7). However, these cases resemble MCD or FSGS in their histopathologic findings and response to glucocorticoids.

The mesangial disease characteristic of class II lupus nephritis, the most common light and immunofluorescence microscopy feature in lupus podocytopathy, does not require specific immunomodulatory therapy directed to the kidney, such as tacrolimus, mycophenolate, or azathioprine. Rather, conservative nonimmunomodulatory therapy is appropriate for patients with these findings on kidney biopsy, usually *via* optimal control of BP through blockade of the renin-angiotensin-aldosterone system. Given her current pregnancy, such medication is contraindicated. After delivery, however, this patient should be started on the maximal dose of an ACE inhibitor or ARB that her BP can tolerate.

In 2002, two small case series (8,9) reported MCD or FSGS occurring in the background of a lupus diagnosis. Eight of the 18 patients in these reports had mesangial deposits, however, including seven of 11 with MCD and one of seven with FSGS, consistent with concurrent mesangial LN (class I and II). The patients with MCD universally showed rapid remission of nephrotic syndrome with steroid therapy; the response to steroids was inconsistent in patients with FSGS lesions. In 2005, Kraft *et al.* (10) reported eight additional patients with SLE, nephrotic syndrome, and light microscopic findings of MCD, FSGS, or mesangial proliferative GN. These authors argued that the development of nephrotic syndrome in patients with lupus was a distinct form of lupus nephritis—hence the term lupus podocytopathy—rather than the coexistence of idiopathic MCD or FSGS and lupus. The current criteria to diagnose lupus podocytopathy are fairly simple and straightforward: (*1*) clinical presentation of nephrotic syndrome in a patient with lupus, (2) diffuse and severe foot process effacement on electron microscopy, and (*3*) the absence of subendothelial or subepithelial immune deposits on light, immunofluorescence, and electron microscopy (11). An altered systemic cytokine milieu rather than immune complex deposition is thought to mediate direct podocyte injury in these patients.

In the most recent and largest retrospective study of this entity, Hu *et al.* (7) presented 50 patients with cases classified as lupus podocytopathy from a 14-year biopsy registry (2000–2013). These cases represented 1.3% of all lupus nephritis biopsies read at Nanjing University during this time period. The remission rate with immunosuppression in this cohort was 94%, with a median time to remission of 4 weeks. As with podocytopathies not associated with lupus, relapse rates were high, occurring in more than one half of the patients. Importantly, response and relapse rates differed among the histologic subtypes: all of the patients with MCD and 27 of the 28 patients with mesangial proliferative GN responded, whereas nonresponders were disproportionately high in the FSGS subgroup.

This patient would, therefore, have a high likelihood of responding to steroids within 4 weeks of therapy initiation, and a taper over the course of her pregnancy would then be appropriate. The use of high-dose steroids during pregnancy will impart an increased risk of gestational diabetes for this patient. In a patient with lupus podocytopathy considered particularly susceptible to either gestational or steroid-induced diabetes (*e.g.*, prior episode of gestational or steroid-induced diabetes or morbid obesity), a calcineurin inhibitor could be used as a steroid-sparing first-line therapy, which has been done in patients with MCD and FSGS who do not want to be exposed to high-dose prednisone (12). In the absence of those particular risk factors, which is the case with this patient, addition of a calcineurin inhibitor would only be indicated

in the event of a relapse of proteinuria during or after the steroid taper.

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Disclosures

None.

References

1. Sethi S, Haas M, Markowitz GS, D'Agati VD, Rennke HG, Jennette JC, Bajema IM, Alpers CE, Chang A, Cornell LD, Cosio FG, Fogo AB, Glassock RJ, Hariharan S, Kambham N, Lager DJ, Leung N, Mengel M, Nath KA, Roberts IS, Rovin BH, Seshan SV, Smith RJ, Walker PD, Winearls CG, Appel GB, Alexander MP, Cattran DC, Casado CA, Cook HT, De Vriese AS, Radhakrishnan J, Racusen LC, Ronco P, Fervenza FC: Mayo clinic/renal pathology society consensus report on pathologic classification, diagnosis, and reporting of GN. *J Am Soc Nephrol* 27: 1278–1287, 2016
2. Wilhelmus S, Alpers CE, Cook HT, Ferrario F, Fogo AB, Haas M, Joh K, Noël LH, Seshan SV, Bruijn JA, Bajema IM: The revisited classification of GN in SLE at 10 years: Time to re-evaluate histopathologic lesions. *J Am Soc Nephrol* 26: 2938–2946, 2015
3. Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW: Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. *CMAJ* 157: 715–725, 1997
4. Bomback AS, Appel GB: Updates on the treatment of lupus nephritis. *J Am Soc Nephrol* 21: 2028–2035, 2010
5. Piccoli GB, Daidola G, Attini R, Parisi S, Fassio F, Naretto C, Deagostini MC, Castelluccia N, Ferraresi M, Roccatello D, Todros T: Kidney biopsy in pregnancy: Evidence for counselling? A systematic narrative review. *BJOG* 120: 412–427, 2013
6. Corapi KM, Chen JLT, Balk EM, Gordon CE: Bleeding complications of native kidney biopsy: A systematic review and meta-analysis. *Am J Kidney Dis* 60: 62–73, 2012
7. Hu W, Chen Y, Wang S, Chen H, Liu Z, Zeng C, Zhang H, Liu Z: Clinical-morphological features and outcomes of lupus podocytopathy. *Clin J Am Soc Nephrol* 11: 585–592, 2016
8. Dube GK, Markowitz GS, Radhakrishnan J, Appel GB, D'Agati VD: Minimal change disease in systemic lupus erythematosus. *Clin Nephrol* 57: 120–126, 2002
9. Hertig A, Droz D, Lesavre P, Grünfeld JP, Rieu P: SLE and idiopathic nephrotic syndrome: Coincidence or not? *Am J Kidney Dis* 40: 1179–1184, 2002
10. Kraft SW, Schwartz MM, Korbet SM, Lewis EJ: Glomerular podocytopathy in patients with systemic lupus erythematosus. *J Am Soc Nephrol* 16: 175–179, 2005
11. Bomback AS, Markowitz GS: Lupus podocytopathy: A distinct entity. *Clin J Am Soc Nephrol* 11: 547–548, 2016
12. Laurin LP, Gasim AM, Poulton CJ, Hogan SL, Jennette JC, Falk RJ, Foster BJ, Nachman PH: Treatment with glucocorticoids or calcineurin inhibitors in primary FSGS. *Clin J Am Soc Nephrol* 11: 386–394, 2016

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