Lupus Podocytopathy: A Distinct Entity

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More than one half of all patients with SLE will have clinically evident kidney disease, generally termed lupus nephritis (LN), at some point during their disease course. The diagnosis and management of LN have improved remarkably over the last three decades enhanced by (*1*) a refined and reproducible classification scheme for the diverse glomerulopathies associated with SLE, (*2*) a number of epidemiologic studies highlighting LN subgroups at increased risk for poor outcomes, and in contrast to other glomerular diseases, (*3*) a consistent record for well performed randomized trials evaluating induction and maintenance therapies (1). Still, there remain subgroups of patients with LN that remain poorly categorized, and these pockets of disease can confound the diagnosing renal pathologist and treating clinical nephrologist.

In 2002, Dube *et al.* (2) and Hertig *et al.* (3) described small series of patients with SLE, nephrotic syndrome, and biopsy findings of minimal change disease (MCD) or FSGS. Eight of 18 patients in these reports had mesangial deposits, including seven of 11 with MCD and one of seven with FSGS, consistent with concurrent mesangial LN (class 1 or 2). 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.* (4) reported eight additional patients with SLE, nephrotic syndrome, and light microscopic findings of MCD (*i.e.*, normal appearing), FSGS, or mesangial proliferative GN. Kraft *et al.* (4) argued that the "development of nephrotic-range proteinuria in patients with SLE without peripheral immune aggregate deposition or endocapillary proliferation on renal biopsy is more likely a manifestation of SLE than the coexistence of idiopathic minimal-change glomerulopathy and SLE" (4). The term lupus podocytopathy thus arose to describe these lesions as part of the LN spectrum.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Hu *et al.* (5) present 50 patients who they have classified as having lupus podocytopathy, culled from a 14-year biopsy registry (2000–2013) and representing 1.3% of all LN biopsies read at Nanjing University during this time period. Thirteen patients had normal light microscopy findings, 28 showed mesangial proliferative changes, and nine had FSGS lesions; 47 of the 50 patients had mesangial immune deposits as confirmed by immunofluorescence and electron microscopy. All of the patients had full nephrotic syndrome with ≥50% (and in most patients, >70%) foot process effacement. This series emerges as the largest cohort of lupus podocytopathy and provides representative data on clinical presentations, treatment responses, and relapse rates in patients with this entity. For example, the remission rate with immunosuppression of 94% is not altogether surprising on the basis of prior series, but the median time to remission of 4 weeks adds a new layer of important, clinically relevant information. 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 changes responded, whereas nonresponders were disproportionately high in the FSGS subgroup. Similarly, AKI was over-represented in the FSGS group (78%) compared with the MCD and mesangial proliferative groups (23% and 25%, respectively). As with podocytopathies not associated with SLE, relapse rates were high (56%) and did not differ by histologic pattern.

A finding that emerges in this series, as in prior reports, is that, in the setting of SLE and lupus podocytopathy, morphologic findings of FSGS are associated with a distinctly more dismal prognosis. Specifically, patients with FSGS compared with those with MCD or mesangial proliferative changes had higher rates of hypertension and AKI on clinical presentation and more severe tubulointerstitial involvement on biopsy. In follow-up, the patients with FSGS not only were less likely to respond to therapy, but when responses did occur, the remissions happened at a median of 8 weeks (compared with 4 weeks for the other subgroups). In contrast, the strikingly similar clinical presentation, remission rates, rapidity of remission, and relapse rates in the MCD and mesangial proliferative subgroups argue against significant differences between these subtypes. These observations raise the question of whether it is appropriate to use the same umbrella term of lupus podocytopathy for all three of these patterns of glomerular injury. One of the limitations of the series by Hu *et al.* (5) is that their results may not apply to non-Asians, and this nongeneralizability could have its biggest effect in the patients with FSGS patterns. For example, a black patient with SLE and FSGS could have lupus podocytopathy but, just as plausibly, could have SLE with concomitant apolipoprotein L1 (*APOL1*) nephropathy (6).

Hu *et al.* (5) propose criteria for diagnosing lupus podocytopathy on the basis of clinical presentation and hallmark biopsy findings on light microscopy, immunofluorescence microscopy, and electron microscopy.

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Table 1. Proposed criteria for diagnosis of lupus podocytopathy

Parameter	Features
Clinical	Diagnosis of SLE by ACR criteria; full nephrotic syndrome (*i.e.*, nephrotic-range proteinuria, hypoalbuminemia, and edema)
Light microscopy	Normal glomeruli or FSGS; mesangial proliferation permitted; endocapillary proliferation, necrosis, and/or crescents not permitted
Immunofluorescence microscopy	Deposits absent or confined to mesangium
Electron microscopy	Diffuse and severe foot process effacement (typically >70%); deposits absent or confined to mesangium

ACR, American College of Rheumatology.

The commonly used International Society of Nephrology/Renal Pathology Society classification of LN does not include lupus podocytopathy. In our practice, we use fairly simple criteria to diagnose lupus podocytopathy: (*1*) clinical presentation of full nephrotic syndrome in a patient with SLE, (*2*) diffuse and severe foot process effacement, and (*3*) the absence of subendothelial or subepithelial immune deposits (Table 1). Mesangial deposits and mesangial proliferation are not part of the criteria; if these findings are present, then the additional diagnosis of mesangial proliferative LN (LN class 2) is merited. If mesangial deposits are not accompanied by mesangial proliferation, the diagnosis of minimal mesangial LN (LN class 1) is rendered. In this manner, we separate the classic forms of immune complex–mediated LN from lupus podocytopathy, with a willingness to diagnose both in the appropriate situation, and we avoid the need for a mesangial proliferative category of lupus podocytopathy. We also subdivide lupus podocytopathy into patients who would otherwise meet criteria for MCD or FSGS, including the morphologic subtypes of FSGS (collapsing, tip lesion, *etc.*). The criteria proposed by Hu *et al.* (5) are similar to what we propose, with the exception of our preference to separate out the findings of mesangial LN (LN class 1 or 2), thus eliminating the mesangial proliferative pattern of lupus podocytopathy. The differences are small.

The report from Hu *et al.* (5) is an important contribution that brings us closer to recognizing and understanding the entity of lupus podocytopathy. The process of developing consensus diagnostic criteria should be straightforward. At present, data supporting an association between MCD and FSGS with SLE are limited to the observation that these entities seem to be more common in SLE and are often present in the setting of a lupus flare; a goal for the future will be to connect these entities in more than an observational manner. Another important question is whether lupus podocytopathy will be added to the next revision of the classification of LN (7). For now, and in significant part because of the contribution of the work by Hu *et al.* (5), we have reached the point that lupus podocytopathy should be considered a distinct and recognizable disease entity.

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Disclosures

None.

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See related article, "Clinical–Morphological Features and Outcomes of Lupus Podocytopathy," on pages 585–592.