

Recent Advancements on Lupus Podocytopathy: A Rising Entity of Nonimmune Complex-Mediated Nephropathy Associated with Systemic Lupus Erythematosus

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Abstract

Lupus nephritis (LN), a common and serious complication of systemic lupus erythematosus (SLE) is considered as a typical immune-complex mediated disease, and currently classified into 6 classes, primarily based on histologic findings of glomerular involvement, which became accepted worldwide for diagnosis, prognosis, and treatment guide. In recent years, a rising numbers of cases are reported to have a nonimmune complex-mediated glomerular podocytopathy among SLE patients presenting with nephrotic syndrome. The kidney biopsy done in those patients showed some with minimal change disease-like features, some with mesangial proliferation and some with focal segmental glomerulosclerosis on light microscopy (LM), but all with diffuse foot process effacement (FPE), and no glomerular capillary proliferation/inflammation on LM as seen in class III and IV LN and no glomerular capillary immune deposits on immunofluorescence (IF) study, observed in class V LN, suggestive of podocyte injury caused by a nonimmune complex mediated pathway, called as “lupus podocytopathy”. Although it is not accepted as a class of LN, the case of lupus podocytopathy of non-immune complex origin is growing and emerging as a distinct entity, of active lupus nephritis, since lupus podocytopathy usually occurs concurrently with extrarenal and active serologic activity, and mostly within 6 months of SLE onset.

Systemic lupus erythematosus (SLE) is an immune-mediated, typical immune complex-associated, inflammatory disease which most commonly involves the skin, joints, and kidneys. The care for patients with SLE is often initiated by rheumatology, but often concerted by dermatology and nephrology services. The term lupus erythematosus is meant for the skin involvement and lupus nephritis for the involvement of the kidneys.

Lupus nephritis (LN), a serious complication of SLE may be diagnosed on the bases of clinical manifestation and clinical markers, however the confirmation and classification require kidney biopsy, and the histologic finding of immune-complex mediated glomerular injury is considered as a hallmark. The current worldwide-accepted classification is the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification based on histologic findings on LM and IF, which was updated in 2018^{1,2}. According to 2018 ISN/RPS classification, class I: minimal mesangial LN, with mesangial immune deposits on IF, but normal

glomeruli on LM. Class II: mesangial proliferative LN, with purely mesangial hypercellularity on LM. Class III: focal LN, involving < 50% of glomeruli and class IV: diffuse LN, both endocapillary and/or extracapillary proliferative findings on LM and with endothelial /mesangial immune deposits on IF. Class V: membranous LN, with subepithelial and/or intramembranous immune deposits, with or without mesangial deposits on IF. Class VI: advanced sclerosing LN, with globally sclerosed without residual activity in > 90% of glomeruli².

Newly emerging cases of SLE patients presenting with Nephrotic Syndrome (NS) in association mostly with active SLE, and predominantly with foot process effacement (FPE) of podocytes on EM, but unlike class III and IV LN, no endocapillary proliferation/inflammation on LM, and unlike class V LN, no glomerular capillary immune deposits on IF have been reported. In 2005, Kraft et al³ described this subset of 8 patients who did not have class III, IV, V or VI LN findings on LM and no immune deposits in glomerular capillaries on IF, but all with diffusely effaced foot processes on EM, not like class I or class II LN, suggestive of podocyte injury by a non-immune complex-mediated mechanism and called it as "lupus podocytopathy". Rare case reports of minimal change disease (MCD) in patients with SLE appeared in 1980's Japanese literature⁴ and in 1990's English literature⁵.

In 2002, Dube et al⁶ reported 7 patients with SLE who presented in full nephrotic syndrome with kidney biopsy findings of diffuse FPE of podocytes in the absence of significant glomerular capillary wall immune deposits, consistent with MCD. In addition, 5 of these 7 patients had mild mesangial proliferation consistent with underlying class II LN. The authors however cautioned against interpreting those 5 cases as an atypical presentation of class II LN, since the isolated mesangial change seen in those cases appears insufficient to account for diffuse FPE and nephrotic syndrome but explained those 5 cases likely have superimposition of MCD entity to class II LN analogous to the occurrence of MCD in patients with mesangial proliferative IgA nephritis⁷. In 2016, Hu et al⁸ reported 50 cases of lupus podocytopathy out of 3,750 kidney biopsies from SLE patients, with features of MCD in 13 of 50 cases, mesangial proliferation in 28 of 50 cases and focal segmental glomerulosclerosis (FSGS) in 9 of 50 cases. Clinical features based on Hu et al⁸ series (the largest among reported series) include nephrotic syndrome in all patients (50 out of 50 patients), average 5-month's duration of SLE, hypertension in 9 of 50 (18%), acute kidney injury in 17 of 50 (34%) specially in FSGS group, low serum complement (C3) level in 34 of 50 (68%). Forty-seven patients achieved remission with immunosuppressive therapy and relapse occurred in 28 patients (60%). The clinical outcome was much more favourable in patients with MCD-like and mesangial

proliferative groups than in patients with FSGS features. The patients with lupus podocytopathy (LP), specially with MCD or mesangial proliferative features usually responded to glucocorticoids, with a median time to remission of 4 weeks. However, there is a high rate of relapse^{3,6,8}.

Podocyte is the visceral epithelial cell with its foot processes covering the glomerular capillary wall, forming main barrier preventing proteinuria, and podocyte injury causes effacement of foot processes, disrupting its slit diaphragm connecting foot processes, which produces proteinuria. A recent report describes podocyte-secreted angiopoietin-4 molecule induced by podocyte injury mediates proteinuria in MCD⁹. In lupus nephritis, podocyte injury can occur not only by glomerular capillary lesions due to immune complex-induced and inflammatory processes¹⁰, but also can be a direct target¹¹, although the exact mechanism causing lupus podocytopathy remains unclear. There is growing evidence that podocytes are immunologically active cells¹². Even though controversial, B7-1 (CD-80) involved in T cell costimulation is found to be up-regulated in podocytes via TLR-4 activation by lipopolysaccharides (LPS)¹³. Podocytes also may participate actively as an antigen presenting cell in immune mediated glomerular disease¹⁴. In addition, podocytes may contribute to the inflammatory response in LN by secreting proinflammatory cytokines¹⁵.

In lupus podocytopathy (LP), no immune deposits in glomerular capillary walls on IF, with foot process effacement of podocytes on EM points a similar pathogenic mechanism speculated for MCD or primary FSGS, independent of a typical immune complex-mediated injury, but likely due to podocyte injury caused by cytokines, lymphokines, or T-cell dysfunction¹⁶.

In lupus nephritis, transformation from one class to another class of immune complex mediated glomerular lesions is often found on serial kidney biopsies. There are also documented transformations between non-immune complex-mediated lupus podocytopathy (LP) to immune complex forms of lupus nephritis (LN). In Hu et al's series⁸, the second kidney biopsy done on 13 relapsed cases out of 50 LP patients, 6 out of 13 transitioned to an immune complex-mediated form of LN (3 to class IV LN, another 3 to class V LN). Perkis et al reported a case who developed MCD (LP) 5 years later after successful treatment of class III (focal proliferative) LN¹⁷, and another case of class V (membranous) LN developed recurrent NS 6 years later with histologic findings of MCD, a non-immune complex-mediated lupus podocytopathy along with features of healed class V LN on the repeated biopsy¹⁸.

We have now a growing number of case reports and rising awareness of lupus podocytopathy. Although it is not accepted as a class of lupus nephritis in 2018 ISN/RPS

classification, LP is emerging as a distinct entity, and one of the proposed diagnostic criteria for LP¹⁹ is (a) clinical presentation of full nephrotic syndrome in a patient with SLE, (b) diffuse foot process effacement, and (c) the absence of subendothelial or subepithelial immune deposits.

We believe that lupus podocytopathy is a distinctive entity and a manifestation of an active lupus nephritis, since it usually occurs concurrently with extrarenal and active SLE serologic finding^{3, 8, 20}, and mostly within 6 months of SLE onset⁸.

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None

Conflict of Interest

None to declare

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any parts of this work are appropriately investigated and resolved.

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