Clinical–Morphological Features and Outcomes of Lupus Podocytopathy

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Abstract

Background and objectives Lupus podocytopathy, which is characterized by diffuse foot process effacement without peripheral capillary wall immune deposits and glomerular proliferation, has been described in SLE patients with nephrotic syndrome in case reports and small series. This study aimed to better characterize the incidence, clinical–morphologic features, and outcomes of such patients from a large Chinese cohort.

Design, setting, participants, & measurements Lupus podocytopathy was identified from 3750 biopsies of SLE patients obtained from 2000 to 2013 that showed mild glomerular histology in patients with a clinical sign of nephrotic syndrome. The biopsy results were divided into three groups: glomerular minimal change, mesangial proliferation, and FSGS.

Results Fifty (1.33%) cases were identified as lupus podocytopathy and included minimal change in 13 cases, mesangial proliferation in 28 cases, and FSGS in nine cases. Extensive foot process effacement appeared in all the biopsies and mesangial electron-dense deposits were present in 47 biopsies. All patients demonstrated nephrotic syndrome, and the median proteinuria was 5.72 g/24 h (interquartile range [IQR], 3.82, 6.92). Seventeen (34%) cases presented with AKI. Forty-seven (94%) patients achieved remission after immunosuppressive therapy for a median time of 4 weeks (IQR, 2, 8). Compared with the patients with minimal change and mesangial proliferation, patients with FSGS showed significantly higher incidence of AKI and severe tubule–interstitial injury and a much lower complete remission rate. During follow-up of a median of 62 (IQR, 36, 84) months, renal relapses occurred in 28 (59.6%) patients. No patient died or developed ESRD.

Conclusions The findings from this cohort study suggest that lupus podocytopathy may represent a special entity of lupus nephritis with distinct clinical–morphologic features. The differences in AKI incidence, tubular injury severity, and response to treatment between the patients with minimal change/mesangial proliferation and those with FSGS patterns indicate two different subtypes of lupus podocytopathy.


Introduction

Nephrotic syndrome (NS) is a common sign of lupus nephritis (LN), which is usually associated with immune complex deposition in the glomerular capillary wall and is frequently accompanied by endocapillary proliferation or necrosis. NS is particularly characteristic of proliferative LN (class III, class IV) or membranous LN (class V) (1,2). However, it was observed 20 years ago that a subset of SLE patients who presented with NS were found to have normal glomeruli or only mild glomerular mesangial proliferation (3–8). In these patients, the most prominent electron microscopy (EM) findings were diffuse foot process effacement (FPE) without immune deposits in the wall of peripheral capillaries, suggestive of podocytopathy. Except for immune deposits in the mesangial region, glomerular podocytopathy in these patients shared similar characteristics with minimal change disease (MCD) (3), which was previously classified as SLE with idiopathic MCD (4–8).

Accumulated evidence from clinical and epidemiologic studies suggested that MCD in these patients was indeed related to SLE (9,10), rather than concomitant with SLE. According to subsequent reports, SLE patients who presented with NS also showed mesangial proliferation (MsP) (11–14), FSGS, or even collapsing FSGS (15,16). These patients shared common features of podocytopathy, which was called SLE-related podocytopathy or lupus podocytopathy (17,18) and might be a distinct class of LN (19,20). However, this class of LN is not included in the current classification of LN.

Patients with lupus podocytopathy have been presented in case reports or small series over the last 20 years (3–22). The prognosis of these patients remains uncertain. In this study, we retrospectively analyzed the epidemiology, clinical–histologic features, treatment response, and long-term outcomes of the patients with lupus podocytopathy in a large cohort of Chinese SLE patients, and compared the
differences among three histologic patterns of lupus podocytopathy: MCD, MsP and FSGS.

Materials and Methods

Patients
A cohort of 3750 Chinese adult SLE patients who met the American Rheumatologic Association criteria for the diagnosis of SLE (23) and underwent first-time renal biopsy at Nanjing Jinling Hospital from January 2000 to December 2013 were retrospectively reviewed and screened for lupus podocytopathy (Figure 1). Patients who fulfilled the following four criteria were classified as having lupus podocytopathy and included in this study: (1) a morphologic pattern resembling MCD, MsP, or FSGS by light microscopy (LM) and immunofluorescence showing mesangial immune deposition; (2) the presence of FPE>50% by EM; (3) the absence of LN class III, IV, and V (including class III/IV+V); and (4) the presence of NS and negative histology of nephrotoxic mediations (17). For biopsies showing an FSGS pattern, glomerular scars of sclerosing class III LN were excluded. This study was approved by the institutional review board of Jinling Hospital, Nanjing University School of Medicine, China.

Renal Morphology
All renal biopsy specimens were processed for LM, immunofluorescence and EM according to standard techniques. For immunofluorescence, 3 μm cryostat sections were stained with FITC-conjugated rabbit anti-human IgG, IgM, IgA, C3 and C1q. For each biopsy, a percentage estimate of FPE was performed by an experienced renal pathologist who examining at least ten distinct fields in nonsclerotic glomeruli under a transmission electron microscope.

The extent of MsP was described as none (<3 mesangial cells per mesangial area), mild (3–4 mesangial cells per mesangial area), moderate (5–6 mesangial cells per mesangial area), and severe (≥6 mesangial cells per mesangial area) (17). Tubular epithelial brush-border loss, tubular cell necrosis, and interstitial edema/inflammatory cell infiltration were described as acute tubular–interstitial lesions, whereas tubular atrophy and interstitial fibrosis were considered as chronic tubular–interstitial lesions. Acute or chronic tubular–interstitial lesions were graded as mild (<25%), moderate (25%–50%) and severe (≥50%) according to the extent of renal tubular interstitial damage.

The LN classes were classified according to ISN/RPS 2003 criteria (24). Lupus podocytopathy was divided into three groups according to morphologic features: MCD (characterized by normal glomeruli or minimal MsP [4–8]), MsP (defined as ≥3 mesangial cells per mesangial area [11–14]), or FSGS (at least one segmental solidification of the glomerular tuft with accumulation of extracellular matrix, hyalinosis and foam cells could be present). Collapsing FSGS was defined by the presence of segmental capillary tuft collapse in at least one glomerulus with overlying podocyte hyperplasia and/or hypertrophy (25). The glomerular segmental scar of proliferative LN was differentiated from FSGS pattern by morphologic features.

Clinical and Laboratory Data
Gender, age, and clinical data were retrieved for all patients. Laboratory examinations included serum albumin, serum creatinine (Scr), serum autoantibodies, C3 and C4. Urinalysis included 24 hour urinary protein excretion and urinary sediment. The following definitions were used: AKI, an increase in Scr of at least 0.3 mg/dl or 50% of the baseline value within 48 hours (26); hypertension, blood pressure >140/90 mmHg; low serum C3, serum C3 <0.8 g/L; low serum C4, serum C4 <0.1 g/L; NS, urinary protein ≥3.5 g/24 h with serum albumin <30 g/L, and peripheral edema.

Treatment Regimens
The patients received glucocorticoids or glucocorticoids plus other immunosuppressive agents for inducing and maintaining remission. The prednisone induction dose was 30–60 mg/d, which lasted for 12 weeks or until 2 weeks after complete remission (CR), and then that the dose was tapered gradually to 10 mg/d for maintenance. The additional immunosuppressive agents included cyclophosphamide, tacrolimus, mycophenolate mofetil, tripterygium glycosides (extracted from traditional Chinese herb Tripterygium wilfordii, which mainly contains triptolide), aza-thioprine, or leflunomide.

Treatment Response and Outcomes
The treatment response was assessed after 12 weeks of induction treatment and was recorded as CR (defined as proteinuria <0.4 g/24 h with normal serum albumin.
level (≥35 g/L) and SCr level (<1.24 mg/dl), partial remission (PR), defined as a decline in proteinuria excretion by >50% of the baseline value and the proteinuria ≥0.4 g/24 h but <3.5 g/24 h, with normal SCr level or an elevation by <15% of the baseline value, and without extrarenal activity), or no response (defined as the absence of CR or PR after 12 weeks of induction treatment). Total remission included CR and PR.

Renal relapse was defined as that in patients with CR who showed proteinuria levels of at least 1.0 g/24 h, or in patients with PR who exhibited an increase of proteinuria by at least 2.0 g/24 h, with or without active urine sediment or increase of SCr by ≥30%. The follow-up period was defined as the time from the renal biopsy to the last follow-up visit (by June 30, 2014). For patients who demonstrated a histologic transition of LN in the second renal biopsy after renal relapse, the follow-up period was defined as the time elapsed from the first renal biopsy to the repeated renal biopsy.

**Statistical Analysis**

Data are presented as median (interquartile range, IQR), or percentages, where appropriate. The Fisher exact test was used to analyze the categorical data. The t-test or Kruskal–Wallis test was used to compare continuous data, using SPSS software for Windows (version 18.0, SPSS Inc., Chicago, IL). A P-value <0.05 was considered to be statistically significant.

**Results**

**Patient Information**

Among the 3750 cases, 50 (1.33%) fulfilled the inclusion criteria of lupus podocytopathy (Figure 1), including 45 females and five males, with a median age of 30 (IQR, 21, 39) years. The median durations of SLE and renal disease were 5 (IQR, 1, 24) and 2 (IQR, 0.7, 4) months, respectively. The median SLE disease activity index was 10 (IQR, 6.5, 13) points. Forty-four (88%) patients presented with NS as the onset symptom of SLE.

### Clinical and Laboratory Findings

Laboratory findings at the time of biopsy are summarized in Table 1. NS was observed in all patients. The median urine protein was 5.72 g/24 h (IQR, 3.82, 6.92). Nine (18%) patients presented with hypertension or microscopic hematuria. Seventeen (34%) patients had concomitant AKI and five of them required renal replacement therapy.

There were no significant differences in the incidence of hematuria and the level of urine protein, serum albumin, serum autoantibodies and serum C4 among the three groups. However, the incidence of AKI was much higher in the FSGS group (seven of nine, 77.8%) than in MCD group (three of 13, 23.1%) and MsP group (seven of 28, 25.0%) (P=0.01), whereas the serum C3 level was much lower in the FSGS and MsP groups than in MCD group (P=0.02 (Table 1).

The extrarenal manifestations are listed in Table 2. Compared with the patients in the MCD and MsP groups, the patients in the FSGS group showed a lower incidence of malar rash and higher incidence of serositis; however, these differences were not significant statistically.

### Renal Morphology

The renal biopsy findings are presented in Table 3. There were 13 biopsies (26%) showing MCD, 28 biopsies (56%)

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### Table 1. Clinical and laboratory findings of patients with lupus podocytopathy

<table>
<thead>
<tr>
<th>Clinical and Laboratory Parameters</th>
<th>Total (n=50)</th>
<th>MCD (n=13)</th>
<th>MsP (n=28)</th>
<th>FSGS (n=9)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>45/5</td>
<td>11/2</td>
<td>25/3</td>
<td>9/0</td>
<td>0.57</td>
</tr>
<tr>
<td>SLE duration, months</td>
<td>5 (1, 24)</td>
<td>4 (1, 10)</td>
<td>10 (1.6, 27.8)</td>
<td>5 (0.8, 33)</td>
<td>0.50</td>
</tr>
<tr>
<td>Duration of renal disease, months</td>
<td>2 (0.7, 4.0)</td>
<td>1 (0.8, 4.5)</td>
<td>3.5 (0.8, 4.0)</td>
<td>1 (0.4, 3.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (18.0)</td>
<td>2 (15.4)</td>
<td>3 (10.7)</td>
<td>4 (44.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>MH</td>
<td>9 (18.0)</td>
<td>0</td>
<td>6 (21.4)</td>
<td>3 (33.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Proteinuria (g/24h)</td>
<td>5.72 (3.82, 6.92)</td>
<td>6.65 (3.82, 9.40)</td>
<td>5.47 (3.81, 6.90)</td>
<td>6.06 (3.68, 6.51)</td>
<td>0.60</td>
</tr>
<tr>
<td>SAlb (g/L)</td>
<td>23.4 (19.6, 27.7)</td>
<td>23.2 (19.6, 27.7)</td>
<td>24.0 (20.4, 26.4)</td>
<td>19.9 (17.6, 28.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>AKI</td>
<td>17 (34.0)</td>
<td>3 (23.1)</td>
<td>7 (25.0)</td>
<td>7 (77.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>SCr (mg/dl)</td>
<td>0.69 (0.56, 1.54)</td>
<td>0.65 (0.60, 0.76)</td>
<td>0.68 (0.54, 1.29)</td>
<td>1.71 (0.86, 2.23)</td>
<td>0.10</td>
</tr>
<tr>
<td>ANA positive</td>
<td>50 (100)</td>
<td>13 (100)</td>
<td>28 (100)</td>
<td>9 (100)</td>
<td>ND</td>
</tr>
<tr>
<td>A-dsDNA positive</td>
<td>13 (26.0)</td>
<td>3 (23.1)</td>
<td>9 (32.1)</td>
<td>1 (11.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>A-Sm positive</td>
<td>16 (32.0)</td>
<td>1 (7.7)</td>
<td>11 (39.3)</td>
<td>4 (44.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>ACL positive</td>
<td>13 (26.0)</td>
<td>5 (38.5)</td>
<td>7 (25.0)</td>
<td>1 (11.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>Low C3a</td>
<td>34 (68.0)</td>
<td>3 (23.1)</td>
<td>23 (82.1)</td>
<td>8 (88.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C3 (g/L)</td>
<td>0.64 (0.45, 0.85)</td>
<td>0.86 (0.80, 1.08)</td>
<td>0.59 (0.41, 0.74)</td>
<td>0.5 (0.48, 0.60)</td>
<td>0.02</td>
</tr>
<tr>
<td>Low C4b</td>
<td>14 (28.0)</td>
<td>3 (23.1)</td>
<td>8 (28.6)</td>
<td>3 (33.3)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Data are expressed as N (%) or median (interquartile range). MCD, minimal change disease; MsP, mesangial proliferation; NS, nephrotic syndrome; MH, microscopic hematuria; SCr, serum creatinine; SAlb, serum albumin; ANA, antinuclear antibody; ND, not done; A-dsDNA, anti-double-stranded DNA antibody; A-Sm, anti-Smith antibody; ACL, anticardiolipin antibody.

*Defined as serum C3<0.8 g/L.

*Defined as serum C4<0.1 g/L.

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showing MsP and nine biopsies (18.0%) showing FSGS (Figure 2, A–C). FSGS of tip lesion, classic, perihilar, and collapsing variants were found in five, two, one, and one biopsies, respectively. According to the current LN classification, 13 MCD cases were preliminarily classified as class I, 28 MsP and seven FSGS cases were classified as class II, and two FSGS cases were unclassified. There were 28 biopsies with acute tubular–interstitial lesions.

Immunofluorescence showed that there were 43 patients with glomerular deposition of both Ig and complements, four patients with only Ig, and three patients without glomerular deposition. Eighteen patients (36.0%) had Ig and/or complement deposition in the cytoplasm of renal tubular epithelial cells or on the renal tubular basement membrane (Figure 2, D and E).

EM showed that FPE ranged from 50% to 95% (median 85%) (Figure 2, F). There were only seven (14%) cases with FPE, 70%. Mesangial electron-dense deposits were observed in 47 biopsies, including 15 biopsies with concurrent rare isolated subendothelial or subepithelial deposits. Dense deposits were not observed in the three patients with negative findings on immunofluorescence.

There was no significant difference in the extent of FPE and glomerular immune deposition pattern among the three groups. The extent of MsP in the MsP and FSGS groups was much more severe than in the MCD group, but all were deemed mild or moderate MsP. The proportion of patients with moderate–severe acute tubular–interstitial lesions was significantly higher in the FSGS group (seven of nine, 77.8%) than in the MCD group (one of 13, 7.7%) or in the MsP group (seven of 28, 25.0%) (P=0.002). The tubular Ig/complement deposition rates were higher in the FSGS group than in the MCD and MsP groups, but the difference was not statistically significant (Table 3).

Response to Treatment and Outcomes
Remission was achieved in 47 (94.0%) patients after induction treatment with glucocorticoids monotherapy (n=30) or glucocorticoids plus other immunosuppressive agents (n=20), including 38 (76.0%) CR and 9 (18.0%) PR;
three patients showed no response. The median time to remission was 4 (IQR, 2, 8) weeks. Renal function recovered to normal in all patients with AKI after induction treatment. The CR rate in the FSGS group (two of nine, 22.2%) was significantly lower than that in the MCD group (12 of 13, 92.3%) and MsP group (24 of 28, 85.7%) (P<0.001). The CR rates were not significantly different between MCD group and MsP group (Table 4).

Patients were followed up for a median of 62 (IQR, 36, 84) months, during which time 28 (56.0%) patients developed renal relapses. Sixteen patients had NS relapse, among whom ten patients had lupus flare with extrarenal manifestation and/or serological activity (elevated serum autoantibody level, or decreased complement level). There was no significant difference in the relapse rate among the three groups. Thirteen relapsed patients had a second renal biopsy, and among them three patients transitioned to class IV and three transitioned to class V. All patients showed normal SCr levels at the last visit. No patients died or developed end stage renal disease.

Discussion

In the present study, we reported a series of 50 SLE patients who presented with NS and mild glomerular lesions. On LM, 28 cases showed MsP, nine cases showed FSGS, and the other 13 cases were minimal change. Immune deposition was demonstrated only in the mesangial region by immunofluorescence and EM. The unique prominent pathologic finding that appeared in all biopsies was extensive FPE, a morphologic characteristic of podocytopathy. A few biopsies showed scattered isolated subepithelial or subendothelial dense deposits, but such deposits might have no correlation with diffuse FPE and NS

Table 4. Treatment response among different groups of lupus podocytopathy

<table>
<thead>
<tr>
<th>Treatment Response and Outcomes</th>
<th>Total (n=50)</th>
<th>MCD (n=13)</th>
<th>MsP (n=28)</th>
<th>FSGS (n=9)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Complete remission</td>
<td>38 (76.0)</td>
<td>12 (92.3)</td>
<td>24 (85.7)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>9 (18.0)</td>
<td>1 (7.7)</td>
<td>3 (10.7)</td>
<td>5 (55.6)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>3 (6.0)</td>
<td>0</td>
<td>1 (3.6)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Time to remission (weeks)</td>
<td>4 (2.8)</td>
<td>4 (2.8)</td>
<td>4 (2.7)</td>
<td>8 (5, 10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Relapse</td>
<td>28 (56.0)</td>
<td>7 (53.8)</td>
<td>15 (53.6)</td>
<td>6 (66.7)</td>
<td>0.86</td>
</tr>
<tr>
<td>Histologic transition</td>
<td>6/13 (46.2)</td>
<td>1/5 (20.0)</td>
<td>3/5 (60.0)</td>
<td>2/3 (66.7)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Data are expressed as N (%) or median (interquartile range). MCD, minimal change disease; MsP, mesangial proliferation.
fore, lupus podocytopathy should be distinguished from most of our patients were classi
ci cal lupus podocytopathy should have FPE
FPE, foot process effacement.
a. Occasional isolated subepithelial or subendothelial dense deposits may be visible. b. Few cases may present with preclinical SLE at the onset of the disease and should be carefully followed up.
pattern (as high as 80%), which was consistent with the finding that the severity of acute tubular–interstitial lesion was mild in both MCD and MsP patterns, but severe in the FSGS group. The patients with MCD and MsP patterns also showed a similar responsiveness to glucocorticoid therapy: they were much more sensitive to glucocorticoid than the patients with FSGS. Previous studies have also reported the low remission rate of lupus podocytopathy with FSGS, especially collapsing FSGS (9,17). For patients with FSGS lupus podocytopathy, induction regimens with glucocorticoid plus other immunosuppressive agents are required to improve the remission rate (9,16,17,32). Although MCD and MsP lupus podocytopathy showed differences in the degree of MsP, it had no correlation with podocyte injury (21). Therefore, we propose that lupus podocytopathy could be further divided into two subtypes, one is the MCD pattern (including MCD and MsP), and the other is the FSGS pattern.

Although our study is the largest cohort of lupus podocytopathy to date, there are still several limitations. First, all patients included in this study are of Chinese Han ethnicity, therefore, our results may not completely apply to non-Asians. It was reported that African patients with lupus podocytopathy have a higher incidences of the FSGS pattern (17). Second, due to the relatively small sample size in each group of lupus podocytopathy, the conclusions need further validation. Third, the comparison of molecular immunology and histology between MCD/MsP LN with and without podocytopathy is required to investigate the pathogenesis of podocyte injury in lupus podocytopathy. In conclusion, the findings in this cohort study suggest that lupus podocytopathy may represent a special entity of LN with distinct clinical–morphologic features. The differences in AKI incidence, tubular injury severity, and response to treatment between the patients with MCD/MsP and those with FSGS indicate that there should be two different subtypes of lupus podocytopathy.

Acknowledgments

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Disclosures

None.

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