Pathogenetic features of severe segmental lupus nephritis

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Abstract

Background. Accumulating evidence supports the notion that the pathogenesis of severe lupus glomerulonephritis is multifactorial and not solely an immune complex-mediated glomerular disease. Alternate mechanisms for glomerular destruction may exist.

Methods. We conducted a retrospective clinicopathologic analysis of 213 patients with lupus nephritis. Twenty-six patients had severe segmental glomerulonephritis (SSGN) and 15 patients had diffuse proliferative glomerulonephritis (DPGN). Patients with pure mesangial lupus nephritis (mesangial glomerulonephritis (MesGN)) (N = 13) were used as histologic controls. The degree of immunologic activity detailed by histologic data including light, fluorescent (IF) and electron microscopy (EM) on kidney biopsies and clinical data from patients with severe lupus nephritis were analysed.

Results. Biopsies from patients with SSGN had fewer glomeruli with wire loops (3 ± 6% versus 35 ± 34% P = 0.005) and hyaline thrombi (0.8 ± 3% versus 16 ± 22%, P = 0.02) compared to DPGN. The amount of IgG by IF was less in SSGN lesions compared to DPGN lesions, and IgG was absent in 30% of the SSGN group compared to none of the DPGN group (P = 0.04). There was no difference in mesangial deposits among the three groups (SSGN, DPGN and MesGN). The EM data supported the IF data. Anti-neutrophil cytoplasmic antibodies (ANCA) were essentially negative in all three groups and the C3 values tended to be lower in DPGN compared to SSGN (48 ± 15 mg/dl versus 60 ± 26 mg/dl, P = 0.09).

Conclusions. The findings in DPGN involve a classic immune complex-mediated glomerulonephritis as demonstrated by the abundant immune aggregates witnessed in the peripheral capillary wall. In contrast, a paucity of peripheral immune aggregates is seen in SSGN implying a different pathogenesis. Our data support a mechanism of glomerular injury in SSGN that is separate from the generally accepted unitary concept of immune complex deposition in lupus nephritis.

Keywords: glomerulonephritis; lupus nephritis; pauci-immune; pathogenesis

Introduction

Lupus nephritis has been considered a prototypical immune complex-mediated glomerular disease. Arguably, the morphologic spectrum of inflammatory glomerular injury has been proposed to represent a continuum that depends on the severity of the immune complex-mediated process [1,2]. Hence, focal segmental glomerulonephritis (FSGN) has been interpreted as being the result of the same immune complex-mediated process as the more extensive lesion of diffuse proliferative glomerulonephritis (DPGN). However, this pathogenetic explanation of the variability of glomerular inflammation has been questioned. In the 1982 World Health Organization classification of lupus nephritis, Churg wrote ‘It is uncertain whether focal lupus nephritis, as defined, is produced by the same immunological mechanism as mesangial and diffuse forms, because in some instances immune deposits are absent from the focal lesion though present elsewhere in the glomerulus’ [3]. This observation was expanded upon by Schwartz et al. in 1983 when they reported four patients with systemic lupus erythematosus (SLE) and necrotizing glomerulonephritis without noticeable subendothelial electron dense deposits and peripheral immune deposits [4]. Subsequent studies revealed histologic and ultrastructural evidence indicating that severe segmental lupus nephritis [World Health Organization (WHO) class III ≥ 50%] was frequently pauci-immune in contrast to diffuse lupus nephritis (WHO class IV) that was characterized by extensive deposition of immune aggregates in peripheral capillary loops [5–8]. The purpose of the present study is to further investigate evidence of disparate mechanisms of glomerular injury in the inflammatory lesions of severe lupus nephritis.
Subjects and methods

Study design and patient selection

This study is a retrospective clinicopathologic analysis of 213 patients with the diagnosis of lupus nephritis who were seen by the Renal Pathology Service and followed by the Division of Nephrology, Department of Medicine at Rush University Medical Center between 1983 and 2007. No referral biopsies were included in this analysis. The biopsies were processed by standard techniques for histology, immunofluorescence microscopy and electron microscopy (EM). All patients fulfilled the American Rheumatology Association criteria for SLE [9,10].

Of the 213 patients identified, 41 biopsies had active lesions in ≥50% of the non-hyalinized glomeruli, as previously defined [11]. The 41 biopsies were dichotomized into those with severe segmental glomerulonephritis (SSGN) involving ≥50% and diffuse global proliferative glomerulonephritis (DPGN). These histological classes are similar to class IV-S (segmental) and IV-G (global) in the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification [12], but there are significant differences. In the WHO classification [11], a segmental lesion can involve any percentage of glomeruli in the biopsy, and there is no limit to the extent of involvement in each glomerulus. Traditionally, the involvement of ≥50% of glomeruli with a segmental lesion has been termed ‘severe FSGN’ [6]. In contrast, the ISN/RPS classification relegates segmental lesions involving over 50% of the glomeruli to class IV-S and those biopsies where >50% of the area of the glomerular tuft is involved are relegated to IV-G.

Consequently, the selection of a widely distributed segmental lesion to ISN/RPS [12] class IV-G has been shown to conceal differences in pathogenesis and prognosis [8]. As the nature of this study is to investigate the pathology of severe lupus nephritis to elucidate insights into pathogenesis, we chose to use descriptive terms of the pathology rather than characterize it into a classification that may obscure information.

SSGN was defined as segmental glomerular endocapillary proliferation or necrosis in ≥50% of the non-hyalinized glomeruli (corresponding to WHO [11] class III ≥50% and ISN/RPS [12] class IV-S if <50% of the glomerular tuft was involved or class IV-G if ≥50% of the glomerular tuft was involved). Individual glomeruli had a range of involvement from only a few capillaries to all but a single lobule in the glomerular cross-section and, rarely, the entire cross-sectional area was involved. Diffuse proliferative lupus glomerulonephritis was defined as involvement of all or almost all glomeruli by global endocapillary proliferation by light microscopy (corresponding to WHO [11] class IV and ISN/RPS [12] class IV-G). We focused on the non-hyalinized glomeruli because we were studying active glomerular damage.

There were 26 biopsies with SSGN and 15 with DPGN. Thirteen biopsies showing pure mesangial lupus nephritis [mesangial glomerulonephritis (MesGN)] were selected as histologic controls and they comprised all cases of pure mesangial lupus nephritis biopsied at our institution. Mesangial lupus nephritis was defined as mesangial hypercellularity and/or expansion without any global or segmental glomerular scars or endocapillary proliferation. Biopsies with FSGN involving <50% of the viable glomeruli, membranous GN and membranous GN coexistent with proliferative GN were excluded. Biopsies with coexisting diabetic nephropathy, severe interstitial nephritis and diffuse global sclerosis were excluded.

Pathology studies

Pathology material from the 41 comparison patients (SSGN and DPGN) and the 13 control patients (MesGN) included glass slides stained for haematoxylin and eosin, periodic acid-Schiff, Masson trichrome and methenamine silver periodic acid-Schiff (Jones stain). All patients had immunofluorescence microscopy photographs and/or EM photographs available for review. Immunofluorescence photographs of 26/26 patients with SSGN, 12/15 patients with DPGN and 13/13 with MesGN were available for review. The EM photographs of 26/26 patients with SSGN, 13/15 patients with DPGN and 13/13 patients with MesGN were available for review. As these were diagnostic biopsies, the electron microscopic material was not sacrificed in order to find electron dense deposits. It is likely that electron microscopic material devoid of electron dense deposits was searched for a longer period of time, thus introducing a possible selection bias for more time evaluating material without obvious deposits in favour of the absence of deposits in these biopsies. Two renal pathologists (MM and MMS) made the original fluorescence observations, graded the intensity of the fluorescence staining using a 0–3+ scale and diagnosed all biopsies. Biopsy adequacy required 10 viable glomeruli.

The histological features that were enumerated included the number of glomeruli showing histologic evidence of the classic signs of glomerular necrosis (karyorrhexis, rupture of the glomerular basement membrane, glomerular fibrin or fibrinoid necrosis), the number of glomeruli with cellular crescents (extracapillary cells more than two layers thick involving ≥25% of the glomerular circumference), the total number of glomeruli, the number of viable glomeruli and the number of glomeruli with segmental or global proliferative lesions. Morphologic evidence of immune aggregate deposition included the presence of hyaline thrombi, wire loops, peripheral capillary wall deposits of immunoglobulin G immune aggregates representing subendothelial deposits, mesangial immunoglobulin G (IgG) immune aggregates and massive subendothelial immune aggregates seen by EM. Subendothelial deposits of immunoglobulin G seen by fluorescence microscopy were non-granular, discontinuous linear deposits with smooth outer contours in the glomerular capillaries, and the immunofluorescence positivity was graded on a scale of 0–3+ by examining photographs of the case. The percentage of glomeruli showing massive subendothelial deposits was based on the proportion of glomerular capillaries examined using EM that had large, circumferential subendothelial electron-dense deposits.

Laboratory and clinical data

Demographic, clinical and laboratory data at the time of renal biopsy were obtained on each patient. Clinical records were reviewed to determine the patients’ age, gender, blood pressure, level of protein excretion, serum creatinine and lupus serologies [anti-nuclear antibody (ANA) titre, anti-deoxyribonucleic acid (anti-DNA) titre, C3, and C4]. Anti-neutrophil cytoplasmic antibody (ANCA) testing was performed by immunofluorescence and, if positive, confirmed by enzyme linked immunosorbent assay (ELISA) at the time of renal biopsy when available.

Statistical analysis

Statistical analysis was performed using ANOVA for continuous variables, and the Fisher exact test for the categorical data. Statistical calculations were performed by the GraphPad Instat® program (San Diego, CA, USA). Data were reported as a mean ± standard deviation and a P < 0.05 was considered significant.

Results

Histology

Light microscopy. The light microscopy histologic features are shown in Tables 1 and 2 and Figures 1 and 2. A greater number of biopsies had glomerular capillary wall disruption in the SSGN group (92%) compared to DPGN (62%). Biopsies with SSGN lesions had significantly fewer wire loops (3 ± 6%) and almost no hyaline thrombi (0.8 ± 3%) compared to DPGN biopsies (wire loops: 35 ± 34%, P = 0.005; hyaline thrombi 16 ± 22%, P = 0.02). Both SSGN (80 ± 15%) and DPGN (98 ± 3%) had >80% active lesions; however, DPGN lesions tended to involve virtually all of the glomeruli (P < 0.001). In comparison, biopsies with MesGN demonstrated no active lesions.

Immunofluorescence microscopy. The immunofluorescence microscopy data are summarized in Table 3. The amount of immune aggregates seen in the peripheral capillary walls significantly differed between the SSGN and DPGN groups (Figure 3). Thirty percent of biopsy specimens with SSGN had no peripheral capillary wall IgG while no DPGN specimens were devoid of IgG (P = 0.04). Only 12% of the SSGN lesions had >3+ IgG staining on IF compared to 75% of the DPGN, demonstrating a significant difference in immune aggregates between these two lesions.
### Pauci-immune lupus nephritis

**Table 1.** Number of biopsies with the histologic finding

<table>
<thead>
<tr>
<th></th>
<th>SSGN</th>
<th>←P→</th>
<th>DPGN</th>
<th>←P→</th>
<th>MesGN</th>
<th>←P versus SSGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>15</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active lesions</td>
<td>26</td>
<td>0.9</td>
<td>15</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Karyorrhexis</td>
<td>20 (78%)</td>
<td>0.7</td>
<td>13 (87%)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>10 (38%)</td>
<td>0.3</td>
<td>3 (20%)</td>
<td>0.2</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Capillary wall disruption</td>
<td>24 (92%)</td>
<td>0.04</td>
<td>8/13 (62%)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Crescents</td>
<td>13 (50%)</td>
<td>0.8</td>
<td>9 (60%)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Wire loops</td>
<td>9 (35%)</td>
<td>0.06</td>
<td>10 (67%)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyaline thrombi</td>
<td>3 (12%)</td>
<td>0.008</td>
<td>8 (53%)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: MesGN = mesangial glomerulonephritis; SSGN = severe segmental glomerulonephritis; DPGN = diffuse proliferative glomerulonephritis.

**P** = *P*-value.

**Table 2.** Percent of glomeruli per biopsy with the histologic finding

<table>
<thead>
<tr>
<th></th>
<th>SSGN</th>
<th>DPGN</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td>Viable gloms/biopsy</td>
<td>19 ± 11</td>
<td>21 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>Active lesions</td>
<td>80 ± 15%</td>
<td>98 ± 3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Karyorrhexis</td>
<td>19 ± 14%</td>
<td>18 ± 15%</td>
<td>0.7</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>6 ± 11%</td>
<td>4 ± 12%</td>
<td>0.3</td>
</tr>
<tr>
<td>Capillary wall disruption</td>
<td>23 ± 18%</td>
<td>17 ± 25%</td>
<td>0.1</td>
</tr>
<tr>
<td>Crescents</td>
<td>9 ± 13%</td>
<td>13 ± 20%</td>
<td>0.6</td>
</tr>
<tr>
<td>Wire loops</td>
<td>3 ± 6%</td>
<td>35 ± 34%</td>
<td>0.005</td>
</tr>
<tr>
<td>Hyaline thrombi</td>
<td>0.8 ± 3%</td>
<td>16 ± 22%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abbreviations: SSGN = severe segmental glomerulonephritis; DPGN = diffuse proliferative glomerulonephritis.

*(P < 0.001).* The intensity of mesangial IgG staining was equal among the three groups (Figure 4).

**EM.** The EM data are summarized in Table 3. It was more common for SSGN to have a complete absence of subendothelial electron dense deposits compared to the DPGN group that had no biopsies devoid of subendothelial immune aggregates. A majority of the SSGN either had small or no subendothelial deposits on EM compared to the DPGN group in which most biopsies revealed extensive subendothelial deposits (Figure 5). Massive subendothelial deposits were considerably less in the SSGN lesions compared to DPGN (*P* = 0.008).

**Clinical characteristics**

The clinical characteristics are reviewed in Tables 4 and 5. The serologic data reflect the presence of anti-DS DNA antibodies and hypocomplementaemia corresponding to the known diagnosis of active lupus nephritis. There was a trend for a lower C3 complement component in the DPGN group although this was not statistically significant (SSGN 60 ± 25; DPGN, 47 ± 15). All groups were predominantly anti-neutrophil cytoplasmic antibody (ANCA) negative.

**Discussion**

We conclude that in severe proliferative lupus nephritis there are at least two mechanisms leading to glomerular damage: a pauci-immune-mediated process leading to the damage occurring in SSGN lesions, and a peripheral capillary wall immune aggregate-mediated process in DPGN lesions. The findings seen on the fluorescence and EM data illustrate the marked difference in capillary wall immune aggregates between the SSGN and DPGN lesions. The scarcity of immune aggregation seen in the peripheral capillary wall in the SSGN lesion defines this lesion as a pauci-immune lesion that is in contrast to the more extensive and conspicuous immune aggregation seen in the peripheral capillary walls of the DPGN lesions. Our data challenge the concept that the degree of inflammatory involvement of the glomerulus, from segmental to global in lupus nephritis, is a continuum of immune complex-mediated disease [1,2]. It is consistent with Dr Churg’s early hypothesis that immune complex-mediated damage is not the exclusive aetiology of glomerular destruction [3].

Our observations are consistent with those previously reported [5–8]. The severe segmental lesion in lupus nephritis, despite displaying minimal immune complex activity compared to DPGN, has demonstrated destructive inflammatory pathology [6,8]. These pathologic findings were also observed by Hill et al. [5], who studied light and immunofluorescence microscopy of 15 patients with segmental and 31 patients with global proliferative lupus nephritis. They noted more immune complexes in the global lesions compared to the segmental, yet the segmental lesions demonstrated a similar amount of crescents and more fibrinoid necrosis [5]. Despite the clear difference between the two lesions, it has also become apparent that global and segmental inflammatory lesions can co-exist in the same glomerulus [7]. Our results expand on these earlier observations, in a different population of patients, with detailed light, fluorescent and electron microscopic data.

Our distribution of patients shows less DPGN versus SSGN when compared to other studies [5,13,14], which could be attributed to our exclusion of referral biopsies. In addition, the way in which the classification of lupus nephritis has changed over time may affect the distribution. The ISN/RPS [12] definitions that separate segmental and global glomerular lesions on the basis of the proportion of glomerular surface area involvement (the two-dimensional projection of the glomerulus on the slide) are significantly different from the 1982 WHO [3] definitions of severe FSGN and diffuse global GN. This recent classification...
changes the way in which severe segmental lesions are distributed between the segmental and global classes, changes the prognosis of the segmental and global lesions and leads to problems in the reproducibility and classification of severe lupus nephritis. SSGN in the 1982 WHO [3] classification (WHO III ≥50%) includes biopsies with segmental lesions irrespective of the extent of glomerular surface area involved (i.e. < and ≥50% of the glomerular surface area), but in the ISN/RPS [12] classification, SSGN (ISN/RPS class IV-S) includes only patients with <50% glomerular surface involvement. Thus, the ISN/RPS [12] classification transfers the most extensively involved segmental lesions (those with ≥50% involvement of the glomerular surface area) from the category of severe FSGN to ISN/RPS class IV-G (diffuse global GN). The way the lesions are classified is a factor that may account for the difference in the spectrum of our patients from those studies [5,13,14] using the ISN/RPS [12] classification. In a well-defined cohort of patients with severe lupus nephritis [8], the lesions were equally divided between segmental (WHO class III ≥50%, 39 cases) and global GN (WHO class IV, 44 cases), but when reclassified using the ISN/RPS [12] criteria, the ratio of diffuse segmental and diffuse global GN (ISN/RPS class IV-S/class IV-G) was 22/61, similar to that observed by others who have reported the classification of severe lupus nephritis using ISN/RPS criteria [5,13,14]. The ratio favouring diffuse global GN in the ISN/RPS [12] classification results from reclassifying and transferring of cases of SSGN with ≥50% glomerular surface area involvement from SSGN into the diffuse global category (ISN/RPS class IV-G). Furness et al. [15] found the same relative increase in IV-G, and they ascribed it to transfers from WHO class III (≥50%) and class V.

The pathogenesis of severe lupus nephritis has classically been described as a complex interplay of immune complexes with free antigen and antibody [16,17]. The severity of glomerular injury despite the lack of immune aggregates in our patients with the SSGN lesions appears to also
Fig. 2. Diffuse global lupus glomerulonephritis—DPGN. (A). The glomerulus is lobulated with global histological features of activity including endocapillary proliferation, hyaline thrombi and wire-loops. The arrow indicates a glomerular capillary that is distended by a hyaline thrombus with an overlying wire-loop. Haematoxylin and eosin, original magnification, 66 ×. (B) The glomerular lobules are outlined by intensely staining discontinuous linear deposits of immunoglobulin G. Note that the deposits have a smooth outer contour because they are packed between the endothelial cell and the continuous glomerular basement membrane, and they correspond to wire-loops seen by light microscopy and large subendothelial deposits seen by electron-microscopy. FITC-rabbit anti-human immunoglobulin G, original magnification 100 ×.

Table 3. Number of biopsies with the immunofluorescence or electron microscopy findings

<table>
<thead>
<tr>
<th></th>
<th>SSGN</th>
<th>alley-P-</th>
<th>DPGN</th>
<th>alley-P-</th>
<th>MesGN</th>
<th>alley-P- versus SSGN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunofluorescence (N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>26</td>
<td>12</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>7 (27%)</td>
<td>0.07</td>
<td>0 (0%)</td>
<td>0.9</td>
<td>1 (8%)</td>
<td>0.9</td>
</tr>
<tr>
<td>1+</td>
<td>3 (12%)</td>
<td>0.5</td>
<td>0 (0%)</td>
<td>0.1</td>
<td>4 (31%)</td>
<td>0.2</td>
</tr>
<tr>
<td>2+</td>
<td>7 (26%)</td>
<td>0.7</td>
<td>4 (33%)</td>
<td>0.4</td>
<td>2 (15%)</td>
<td>0.7</td>
</tr>
<tr>
<td>3+</td>
<td>6 (23%)</td>
<td>0.3</td>
<td>5 (42%)</td>
<td>0.9</td>
<td>5 (38%)</td>
<td>0.5</td>
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<tr>
<td><strong>Peripheral IgG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8 (30%)</td>
<td>0.04</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
<td>11 (85%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Trace</td>
<td>3 (12%)</td>
<td>0.9</td>
<td>1 (8%)</td>
<td>0.9</td>
<td>1 (8%)</td>
<td>0.9</td>
</tr>
<tr>
<td>1+</td>
<td>6 (23%)</td>
<td>0.4</td>
<td>1 (8%)</td>
<td>0.9</td>
<td>0 (0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>2+</td>
<td>6 (23%)</td>
<td>0.4</td>
<td>1 (8%)</td>
<td>0.9</td>
<td>1 (8%)</td>
<td>0.4</td>
</tr>
<tr>
<td>3+</td>
<td>3 (12%)</td>
<td>&lt;0.001</td>
<td>9 (75%)</td>
<td>&lt;0.001</td>
<td>0 (0%)</td>
<td>0.5</td>
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<tr>
<td>Present</td>
<td>11 (44%)</td>
<td>0.9</td>
<td>6 (50%)</td>
<td>0.005</td>
<td>0 (0%)</td>
<td>0.006</td>
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<tr>
<td><strong>Electron microscopy (N)</strong></td>
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<td>26</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
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<tr>
<td>Small</td>
<td>5 (20%)</td>
<td>0.2</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
<td>11 (85%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Massive</td>
<td>10 (38%)</td>
<td>0.008</td>
<td>11 (85%)</td>
<td>&lt;0.001</td>
<td>2 (15%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Abbreviations: MesGN = mesangial glomerulonephritis; SSGN = severe segmental glomerulonephritis; DPGN = diffuse proliferative glomerulonephritis.

Peripheral/mesangial IgG = 1+, 2+ etc. represents intensity of immunofluorescence staining.
P = P-value.

represent a different pathogenesis from the defined immune aggregate-mediated glomerular lesions. The SSGN lesion represents a pauci-immune glomerulonephritis that is generally seronegative for ANCA. This seronegativity for ANCA in the setting of pauci-immune crescentic glomerulonephritis has been described in 10% [18] to 33% [19] of cases of small vessel vasculitis. Pathogenetic processes other than that proposed for ANCA appear to be capable of causing glomerular inflammatory injury. Proliferative and crescentic forms of vasculitis are associated with a delayed-type hypersensitivity response (DTH) in experimental models [20] and could explain the capillary wall disruption seen in the pauci-immune lupus lesion. The DTH response may be initiated by GM-CSF induction of MHC II expression on macrophages leading to the promotion of the cytokine response of T cells towards T helper 1 cells (Th1) [21]. Nephritogenic Th1 cells have been implicated in the DTH seen in experimental models in crescentic forms of GN and are largely absent in classic humorally mediated forms of GN [20]. Murine models have demonstrated that Th1 cells are responsible for the production of IFN-γ that is instrumental in the cell-mediated immune injury seen
in pauci-immune GN [22,23]. This cascade of events may account for the capillary wall damage seen in the human pauci-immune SSGN lupus lesion.

Other mechanisms that are not T-cell dependent have been proposed to explain glomerular crescent formation. Ding et al. [24] have shown that dysregulated epithelial stem cell formation can result from the selective loss of the tumour suppressor Von Hippel-Lindau protein (pVHL). One could speculate regarding the immune event capable of causing podocyte proliferation; however, the mediation of this phenomenon would not necessarily involve T-cell cytokines.

As we have noted, mesangial IgG deposits are frequently observed in SSGN and DPGN. The existence of these mesangial deposits should not serve to confuse the pauci-immune nature of the peripheral capillary lesion seen in pauci-immune GN [22,23]. This cascade of events may account for the capillary wall damage seen in the human pauci-immune SSGN lupus lesion.

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in SSGN. As documented by our observations, extensive mesangial deposits can be present in MesGN without pathological or clinical evidence of active glomerular disease.

Our study confirms that the pathogenic mechanisms involved in severe lupus nephritis are complex and diverse and not solely limited to immune complex-mediated injury. The paucity of peripheral capillary wall immune aggregates in the SSGN lesion suggests a pathogenesis separate from the immune aggregate-mediated lesion seen in DPGN. Recognizing this essential difference in histologic appearance and pathogenesis has implications for classification and for future treatment endeavours in the field of lupus nephritis.

Conflict of interest statement. None declared.

References


Received for publication: 8.7.09; Accepted in revised form: 27.7.09