Immunohistochemical Localization of IL-8 and TGF-β in Streptococcal Glomerulonephritis

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Abstract. Acute poststreptococcal glomerulonephritis (APSGN) is characterized by diffuse glomerular hypercellularity, primarily as a result of accumulation of neutrophils (exudative glomerulonephritis), increase in intrinsic glomerular cells, and transient pathological mesangial matrix expansion. Cytokines and growth factors are supposed to play an important role as mediators of inflammation and as progression factors in various renal disorders. Interleukin-8 is a recently described cytokine, defined as a selective activator and chemotactic factor. This novel cytokine is secreted by intrinsic monocytes stimulated with lipopolysaccharides (LPS) (2,3), and known as a neutrophil attractant of polymorphonuclear leukocytes (PMNL) and transforming growth factor (TGF)-β plays a central role in the accumulation of pathological extracellular matrix in glomerulonephritis. This study analyzed the biopsies of ten patients with APSGN, using immunohistochemistry (avidin-biotin complex/horseradish peroxidase method) using monoclonal antibodies anti-IL-8, anti-TGF-β1, β2, β3. Controls consisted of non-immune mouse serum, or anti-TGF-β preabsorbed with human recombinant TGF-β. Compared with normal renal tissue, and minimal change disease, an increased glomerular IL-8 and TGF-β staining was observed in all of the biopsies. Furthermore, in one patient, we observed a weak deposit of TGF-β in tubulointerstitium. Immunoreactive IL-8 and TGF-β in glomeruli was correlated with light microscopic and clinical features. There was a significant association (P < 0.05), between IL-8 glomerular immunoreactivity and neutrophil infiltration and between TGF-β glomerular staining and mesangial matrix expansion. Otherwise, there was no correlation with the mesangial cellularity. It was concluded that increased protein expression of IL-8 and TGF-β are observed in APSGN and may play a role in the acute glomerular inflammation. (J Am Soc Nephrol 8: 234–241, 1997)

Glomerular hypercellularity in the acute phase of poststreptococcal nephritis is caused predominantly by intraglomerular polymorphonuclear leukocyte (PMNL) (exudative glomerulonephritis) and mononuclear cell infiltration. The recruitment of PMNL to inflammatory sites is dependent, at least in part, on chemotactic factors generated in tissue, such as cleavage products of complement activation C5a and C3b. However, the precise mechanism causing the infiltration of PMNL remains to be investigated.

Recent studies in some human proliferative glomerular diseases, have shown elevated urinary interleukin (IL)-8 levels that correlated with the leukocyte infiltration in glomeruli, suggesting that IL-8, produced in glomeruli, promotes the infiltration of neutrophils (1).

IL-8 is a recently described cytokine, originally purified from the supernatant of human monocytes stimulated with lipopolysaccharides (LPS) (2,3), and known as a neutrophil chemotactic factor. This novel cytokine is secreted by intrinsic glomerular mesangial, endothelial, and epithelial cells (4–6) and also by tubular cells (7).

On the other hand, an important early histological manifestation in acute poststreptococcal glomerulonephritis (APSGN) is the transient mesangial matrix expansion, with or without mesangial hypercellularity. A key role of transforming growth factor-β (TGF-β) in the accumulation of pathological extracellular matrix in an experimental model of acute mesangial glomerulonephritis in rats induced by a single injection of antithymocyte serum, has been shown (8–9). The relevance of these studies to human glomerular diseases has recently been demonstrated, in kidney biopsy specimens from patients with mesangial proliferative glomerulonephritis, (10), diabetic nephropathy (11), and more recently in other chronic glomerular diseases (12).

TGF-β (molecular weight, 25 kD) belongs to a family of multifunctional cytokines that are dimeric proteins (13). TGF-β profoundly alters three processes involved in extracellular matrix deposition: (1) it induces synthesis of numerous extracellular matrix proteins; (2) it decreases matrix degradation by downregulation of proteases and induction of protease inhibitors; and (3) it enhances the expression of integrins on the cell surface, which facilitates the deposition of matrix (14).

The aim of this study was to detect the expression of IL-8 and TGF-β by immunohistochemistry in biopsies of patients with APSGN, and to analyze their association with light microscopic and clinical features.

Materials and Methods

Patients

Ten patients (eight men, two women) with a clinical and immunopathological diagnosis of APSGN were studied. The age range was 11
to 47 yr, with a mean of 25 yr. All of the patients had preceding streptococcal infections; seven had skin infection as a complication of scabies, and three had pharyngeal infection.

All of the patients were admitted to the hospital with diagnosis of acute nephritic syndrome, and renal biopsies were performed as soon as possible, for diagnostic and/or prognostic reasons. The clinical signs of APSGN were sudden appearance of edema, hypertension, oliguria, hematuria, proteinuria, and red cells casts. Six patients had a transient nephrotic-range proteinuria (>3 g/24 h), and the remaining four had moderate or mild proteinuria. All of the patients had elevated serum levels of antistreptolysin O; in addition, serum C4 levels were below normal values during the first month of the disease in eight patients, and C4 levels were in the normal range in six of nine patients tested.

Typical lesions of APSGN were found by light, fluorescence, and electron microscopy in renal tissues obtained by percutaneous biopsy in all of the patients.

**Tissue Specimens**

The tissue was fixed in 4% buffered formalin and embedded in paraffin for light microscopic examination. Sections of 3-μm thicknesses were stained with hematoxylin and eosin, periodic acid-Schiff, and methenamine silver stains. Each biopsy specimen was assessed with respect to the severity of histologic features in the glomeruli (leukocyte infiltration, mesangial cellularity, the increase in mesangial matrix, and the presence of sclerosis, crescents or adhesions), tubules (atrophy and dilation), interstitium (cell infiltration, edema, and fibrosis), and arterioles. Abnormalities were graded semiquantitatively (absent or minimal, mild, moderate, or marked) according to procedures previously described by Pirani (15).

Both sections' collections, namely histologic and immunohistochemical, were analyzed separately in a blinded way, by two different observers. There was almost full correlation between the observers.

**Immunohistochemistry**

Renal tissue was immersed in Tissue-Tek (Miles Laboratories, Elkart, IN), and snap-frozen in liquid nitrogen. Cryostat sections (5 μm) were mounted on poly-L-lysine coated slides. Immunoperoxidase staining was performed by the ABC method (streptavidin-biotin-complex/horseradish peroxidase [HRP] method).

Sections were fixed in acetone at 4°C, air-dried, and then endogenous peroxidase activity was quenched in methanol containing 1% H2O2 at room temperature for 20 min. The sections were washed for 5 min in trisphosphate saline (TPS) followed by a 30-min incubation with normal rabbit serum 1:5 in BSA 0.1%. The sections were then incubated at room temperature overnight with specific anti-TGF-β1,-β2,-β3 (immunoglobulin [Ig] G1) and anti-IL-8 (IgG1) monoclonal antibodies (Immugenex, Los Angeles, CA), diluted 1:30 in antibody diluting buffer (TPS - 0.1% BSA.). After a TPS wash, sections were incubated at room temperature for 30 min with a rabbit anti-mouse IgG biotinylated antibody (Dako E 354, Carpinteria, CA) diluted 1:200 with TPS. Finally, sections were washed and then incubated for 30 min with streptavidin-biotin-peroxidase complex, diluted 1:500 in TPS. The sites of peroxidase activity were visualized by incubation in 0.1% diaminobenzidine 0.03% H2O2 solution for 15 min.

Sections were counterstained with hematoxylin, washed, cleaned, and covered with a glass coverslip.

Negative controls experiments were performed by either (1) replacing the primary antibody with antibody diluting buffer, or (2) replacing the primary antibody with a nonimmune mouse monoclonal (1/30), and (3) preabsorption of the primary mouse monoclonal anti-body anti-TGF-β with human recombinant TGF-β1 (R&D Systems, Minneapolis, MN).

Tissue sections were not treated with acid-urea before the incubation with anti-TGF-β and anti-IL-8 antibodies, to disclose reactive epitope.

Renal tissue obtained from four patients with renal trauma, or renal tumors were used as normal kidney tissue. We also studied the renal tissue obtained from four patients with minimal change disease.

The immunostaining for IL-8 and TGF-β, was graded semiquantitatively as minimal (−), weak and spotty intraglomerular staining (+), moderate and segmental intraglomerular staining (++), or marked with a strong and diffuse intraglomerular staining (+++).

**Statistical Analysis**

The statistical significance (defined as P < 0.05) was evaluated using the contingency table (chi-squared test).

**Results**

The clinical and serological findings in patients with APSGN are shown in Table 1. The mean age was 25 yr (range, 11 to 47 yr), and only two patients were female. There was a transient nephrotic range proteinuria in six of ten cases, with a moderate proteinuria in another three patients. The serum creatinine concentration was slightly increased in six cases.

The presence of IL-8 and TGF-β proteins in nephritic glomeruli was demonstrated by immunohistochemistry with a streptavidin-biotin-peroxidase complex. The grade of immunostaining for TGF-β and IL-8, and the glomerular histologic features are presented in Table 2.

Glomerular IL-8 staining was observed in all the biopsies of nephritic patients; it was strong in four patients (Cases 1, 3, 8, 9), moderate in four patients (Cases 2, 4, 6, 7), and weak in the last two cases (Cases 5, 10). IL-8 protein glomerular immunoreactivity was global and present along the glomerular capillary walls and in the mesangium (Figure 1, Cases 6 and 8).

There was a significant correlation (P < 0.05) between IL-8 glomerular immunoreactivity and the glomerular neutrophil infiltration, as is shown in Tables 2 and 3. Otherwise, this immunostaining did not correlate with the mesangial matrix increase, the mesangial cellularity, and the histologic activity grade. On the other hand, the glomerular IL-8 immunoreactivity was not correlated with the time of the disease elapsed before the biopsy, neither with the magnitude of proteinuria.

We did not find IL-8 immunostaining in tubulointerstitium, and IL-8 was not observed in normal renal tissue (Figure 3). Traces amounts of IL-8 were observed in renal tissue of two controls with minimal change disease.

Glomerular TGF-β staining, was also observed in the biopsies of nephritic patients, and it was strong and prominent in the expanded mesangium in four cases, as is shown in Figure 2 (Cases 6 and 8). In the remaining patients, the staining was moderate in one biopsy (Case 2), weak in Cases 5 and 7, and minimal in Cases 4, 9, and 10. The immunoreactivity was particularly confined to the mesangium and the glomerular capillary walls.

There was a significant association between TGF-β glomerular immunoreactivity (P < 0.05) and the mesangial matrix increase, as is shown in Table 4 and Figure 2. Although there was correlation between histologic activity grade and TGF-β
Table 1. Clinical and serological parameters in APSGN patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Streptococcal Infection</th>
<th>ASOa</th>
<th>C3b (mg/dL)</th>
<th>C4c (mg/dL)</th>
<th>Proteinuria</th>
<th>Creatinine (mg/dL)</th>
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<td>4</td>
<td>18</td>
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<td>8</td>
<td>+</td>
<td>1.5</td>
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</table>

*a Antistreptolysin units.  
*b Normal range, 96 to 150 mg/dL.  
*c Normal range, 17 to 44 mg/dL.  
*d Proteinuria: + = <1.0 g; ++ = 1 to 3 g/24 h; +++ = >3 g/24 h.

Table 2. Glomerular immunostaining for IL-8 and TGF-β and histological findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Biopsy Timea</th>
<th>Neutrophil Infiltrationb</th>
<th>Mesangial Matrixc</th>
<th>Mesangial Cells</th>
<th>Histologic Activityd</th>
<th>IL-8</th>
<th>TGF-β</th>
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<td>–</td>
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<td>+</td>
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<td>+/–</td>
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<td>+</td>
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<td>+</td>
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<td>7</td>
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<td>+</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>52</td>
<td>+/-</td>
<td>44</td>
<td>+</td>
<td>+++</td>
<td>+/–</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>5</td>
<td>+/-</td>
<td>24</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*a Days elapsed between the renal biopsy and the first clinical symptoms, detected by the patient himself.  
b P < 0.05 between neutrophil infiltration and glomerular immunostaining for IL-8.  
c P < 0.05 between mesangial matrix increase and glomerular immunostaining for TGF-β.  
d Graded according to hypercellularity, leukocyte infiltration, mesangium edema, and crescent formation.  
e P < 0.05 between histologic activity and TGF-β expression; P = not statistically significant between histologic activity and IL-8 expression.

Discussion

In this study, the presence of IL-8 and TGF-β was demonstrated in the glomeruli of patients suffering with APSGN, suggesting that IL-8 may be responsible for the leukocyte infiltration, particularly neutrophils into glomeruli, and TGF-β for the mesangial matrix increase, in the acute phase of this disease.

IL-8 is a recently described 6-to 10-kd cytokine, defined as a selective activator and chemoattractant of PMNL and also known as neutrophil chemotactic factor and neutrophil activating peptide-1 (2, 3). There is increasing evidence that IL-8 promotes leukocyte adhesion in vivo and leads to recruitment of PMNL to sites of tissue inflammation (16–18), stimulating their release of lysosomal enzymes and superoxides (19). IL-8 is resistant to many proteases, its secretion requires de novo synthesis, and unlike short-lived chemotactic factors such as complement fragments, stable IL-8 has the potential for longer duration of action at sites of tissue inflammation (20). Furthermore, Taub et al. (21) have recently shown that upon stimu-
Figure 1. Renal biopsies from two patients with acute poststreptococcal glomerulonephritis, which demonstrate presence of IL-8 by immunohistochemistry (Avidin-biotin-[HRP] method). Case 6: (A) Glomerular immunostaining for IL-8; score ++. (Original magnification, ×150.); (B) Detailed magnification of Figure A. (Original magnification, ×300.) Case 8: (C) Glomerular immunostaining for IL-8; score ++++. (Original magnification, ×150.); (D) Detailed magnification of Figure C. (Original magnification, ×300.)

Table 3. Association between glomerular immunostaining for IL-8 and the glomerular neutrophil infiltration in ten cases of APSGN

<table>
<thead>
<tr>
<th>Test</th>
<th>Immunoreactive IL-8</th>
</tr>
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<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Glomerular neutrophil</td>
<td>&lt;13</td>
</tr>
<tr>
<td>infiltration</td>
<td>13 to 24</td>
</tr>
<tr>
<td></td>
<td>&gt;24</td>
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</table>

*P < 0.05.

Neutrophils store and release chemoattractants that mediate T cell and monocyte accumulation at sites of inflammation. In view of these findings, and taking into account the mononuclear infiltration described in this disease, the identification of these cells by modern probes, appears to be an interesting task for future investigations.

Our studies are complementary to the observations of Wada et al. (1), who showed a significant relationship between the leukocyte infiltration in glomeruli and the increased urinary IL-8 levels in non-streptococcal proliferative glomerulonephritis, suggesting that this cytokine was produced locally in the diseased renal tissue. However, their immunohistochemical study for IL-8 was confirmatory only in six of 34 patients with detectable urinary IL-8 studied. We have not measured plasma or urinary IL-8 levels in APSGN, but we have observed glomerular immunostaining for IL-8 in all of the tissues examined, which was significantly associated with the glomerular neutrophil infiltration.

Recently, Garin et al. (22) demonstrated the presence of IL-8...
Figure 2. Immunostaining for TGF-β 1, 2, 3 in renal biopsies from the same two patients with acute poststreptococcal glomerulonephritis, shown in Figure 1 (Avidin-biotin-HRP method). Case 6: (A) Glomerular immunostaining for TGF-β. Score +++. (Original magnification, ×150.); (B) Detailed magnification of Figure A (Original magnification, ×300.); (C) Paraffin section stained with hematoxylin and eosin. The glomerulus appears hypercellular as a result of neutrophil infiltration; a marked mesangial expansion is observed. (Original magnification, ×300.) Case 8: (D) Glomerular immunostaining for TGF-β. Score +++. (Original magnification, ×150.) (E) Detailed magnification of the glomerulus shown at the left in Figure D. (Original magnification, ×300.) (F) Paraffin section, stained with hematoxylin and eosin. The glomerulus appears hypercellular because of a marked neutrophil infiltration; marked mesangial matrix expansion is also observed. (Original magnification, ×300.)

in sera and IL-8 mRNA in peripheral blood mononuclear cells of patients with relapsing minimal change disease, and its effect on sulfate turnover in the glomerular basement membrane, suggesting a possible relationship between IL-8 and increased glomerular permeability to proteins. In our patients, we did not observe a significant association between IL-8 immunoreactivity and proteinuria, although a potential role of IL-8 in the transient proteinuria of these nephritic patients cannot be ruled out.

We postulate that the relevance of our observations in APSGN patients is in relationship with the known effect of IL-8 as a neutrophil chemotactic and activating factor, promot-
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Figure 3. Controls. (A) Frozen section from a normal kidney, processed for the demonstration of IL-8. (Original magnification, ×150.) (B) Frozen section from a patient with a minimal change lesion, processed for the detection of TGF-β. (Original magnification, ×150.)

Table 4. Association between glomerular immunostaining for TGF-β and the mesangial matrix increase in ten cases of APSGN

<table>
<thead>
<tr>
<th>Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+/−</td>
</tr>
<tr>
<td>Mesangial matrix increase</td>
<td>+/−</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>++</td>
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<td>+++</td>
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</table>

* P < 0.05.

ion neutrophil adhesion to endothelium, and causing the release of reactive oxygen metabolites and the degranulation of neutrophils.

On the other hand, glomerular TGF-β immunostaining was also observed in the biopsies obtained from APSGN patients, and it was associated with the histologic activity grading and with the mesangial matrix increase, as defined by the presence of increased amount of periodic acid-Schiff stain–positive material in the mesangial region. TGF-β plays a central role in the accumulation of pathological extracellular matrix in glomerulonephritis (9,23,24). Elevated expression of TGF-β, and its association with increased synthesis of collagens, proteoglycans (biglycan, decorin), and fibronectin, have been reported in experimental models of mesangial proliferative glomerulonephritis (25), anti-glomerular basement membrane nephritis (26), and focal glomerular sclerosis (27).

Increased glomerular TGF-β expression has been observed in patients with diabetic nephropathy, and compared with normal kidney tissue and with patients with minimal change disease and thin basement membrane disease (11). The presence of TGF-β in glomerular mesangium of biopsies from 35 patients with mesangial proliferative glomerulonephritis (including 24 patients with IgA nephropathy) was recently demonstrated by indirect immunofluorescence by Yoshioka and coworkers (10). Additionally, Lai et al. (28) observed a significant correlation between the mesangial staining of TGF-β1 and TGF-β2 and the severity of histopathologic grading according to glomerular and interstitial scleroses in patients with IgA nephropathy.

In our study, the glomerular expression of TGF-β and its significant correlation with the increase in mesangial matrix, correspond to what would have been predicted from the experimental model in rats with acute, reversible glomerulonephritis induced by a single injection of an antibody reactive with glomerular mesangial cells (8,9). In that model of acute mesangial proliferative glomerulonephritis, it was shown that overproduction of TGF-β is the cause of pathologic matrix accumulation in the nephritic glomeruli, which contain more TGF-β1 mRNA than normal glomeruli, synthesize more TGF-β1 protein, and produce much more fibronectin and proteoglycans. The increased production of matrix components reached a peak at 2 wk and returned to basal level by 4 wk. Simultaneously, the pathological matrix began to regress and the glomeruli returned to a histologically normal appearance, such as that described in acute reversible poststreptococcal glomerulonephritis.

We did not perform follow-up biopsies in our group of patients because of their excellent clinical evolution, but is tempting to speculate that nonhealing or histologic and clinic chronicity could be associated with sustained expression of TGF-β. This finding has been demonstrated in an experimental model with repeated injections of anti-mesangial serum, with the appearance of tubulointerstitial TGF-β expression and the development of progressive kidney fibrosis (29). However, only in one patient did we observed a weak tubulointerstitial immunoreactivity, whose significance is unknown.

Alternatively, the possibility must be considered that the immunoreactive TGF-β detected in our APSGN patients corresponds to a latent form. If this were the case, the association between TGF-β and mesangial matrix changes would be only apparent. The cells responsible for the increased TGF-β1,2,3 expression have not been identified, but they could be mesangial cells and/or infiltrating monocyte/macrophages. Early accumulation of platelets and macrophages in damaged glomeruli has been reported in experimental acute glomerulonephritis, and likely contributes to the elevated levels of TGF-β in the initial phase of the disease (29).

In addition to enhanced synthesis of matrix components,
inhibition of matrix degradation could facilitate the accumulation of extracellular matrix in tissues. TGF-β is known to decrease the synthesis of proteases and increase the synthesis of protease inhibitors. One of the proteases strongly influenced by TGF-β is the plasminogen activator/plasmin system (30).

In relation to APSGN, Poon-King et al. recently have identified an extracellular plasmin binding protein from nephrotoxic streptococci, called nephritis plasmin-binding protein (NPBP) (31). On the other hand, the nephrotoxic strains secrete Group A streptokinase (32), which converts human plasminogen to the active plasmin moiety. Therefore, it has been proposed that NPBP binds to plasmin, forming an activated NPBP-plasmin complex, possibly protecting plasmin from inactivation by α2-antiplasmin (31). This hypothesis, if confirmed, could facilitate the resolution of the mesangial matrix accumulation observed in APSGN.

Additionally, it has been recognized that angiotensin II stimulates extracellular matrix protein synthesis through induction of TGF-β expression in glomerular mesangial cells (33). The well-known suppression of the renin-angiotensin system in APSGN, if confirmed, could facilitate the resolution of the mesangial extracellular matrix accumulation observed in APSGN.

In conclusion, we demonstrated an increased immunostaining for IL-8 and TGF-β in glomeruli from patients with APSGN, which may enhance the glomerular neutrophil infiltration and the mesangial matrix, respectively.

Acknowledgments

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References


32. Mezzano S, Burgos E, Mahabir R, Kemeny E, Zabriskie JB: Failure to detect unique reactivity to streptococcal streptokinase in either the sera or renal biopsy specimens of patients with acute poststreptococcal glomerulonephritis. *Clin Nephrol* 38: 305–310, 1992
