The significance of tubulointerstitial nephritis in IgA nephritis

HIDEKAZU SHIGEMATSU, YUTAKA KOBAYASHI*, SUMIO TATENO*, YOSHIYUKI HIKI* and SADAHITO KUWAO**

Department of Pathology, Shinshu University School of Medicine, Matsumoto
Departments of * Medicine and ** Pathology, School of Medicine, Kitasato University, Sagamihara, Japan

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The occurrence of significant tubulointerstitial nephritis (TIN) was observed in 6 (18.3%) of 32 patients with IgA nephritis registered in 1991.

T lymphocytes and macrophages in the interstitium were seen to invade the tubulus through injured tubular basement membrane (TBM), then were seen in the intercellular spaces of tubular cells which showed degeneration, single cell necrosis or detachment. Thus some tubular components were seen destroyed and had disappeared resulting in interstitial fibrosis, and others showed a regeneration process forming a renewed TBM on the innerside of the original TBM. However the recurrence of cellular inflammation was again observed in these regenerated tubuli. Thus the progression of nephron loss by TIN was seen to be independent of the glomerular changes and TIN is considered to be one of the important factors in predicting the prognosis of IgA nephritis.

Introduction

It has been recognized that the grade of renal tubulointerstitial lesions correlates significantly with renal function [1–5] and hence, constitutes one of the important factors for estimating the prognosis of renal disease. Tubulointerstitial lesions, however, exhibit of variable changes, such as cell infiltration and accumulation in the renal interstitium sometimes with tubulitis, and progression to interstitial fibrosis in some cases, the changes are regarded as those of secondary atrophic response to the glomerular lesions. In some primary glomerulonephritides, tubulointerstitial nephritis (TIN) has been known to develop independently of glomerulitis [6]. In IgA nephritis, the study of TIN has not been fully undertaken. Since IgA nephritis is the most common glomerular disease in Japan, the analysis of TIN will also be necessary for prognostic histopathological estimation of this renal disease in addition to the evaluation of glomerular lesions.

Materials and methods

Thirty-two cases were diagnosed as IgA nephritis in Kitasato University Hospital in 1991, and renal biopsy specimens of those patients were used for histopathological analysis of glomerulitis and TIN. For the study of glomerular lesions, a “histological activity index of IgA nephritis” [7] was used. Briefly, the evaluation of histological activity was focused on the amount of acute and chronic lesions in intra- and extra-capillary changes. The lesions were graded and given a value ranging from none (0) through, mild (1) and, moderate (2) to marked (3) according to the amount and frequency of the lesions. These values were added and the product used as acuteness and chronicity indices (0–6). In addition to routine immunofluorescent microscopic study for immunoglobulins, complements and fibrin/fibrinogen on the frozen sections, immunohistochemical study was performed using peroxidase-antiperoxidase method (PAP) on the paraffin-embedded renal tissue of cases with significant tubulointerstitial lesions. Antibodies applicable to paraffin sections were CD34, L26, UCHL-1, CD68 (DAKOPATTS, Denmark), IgA (Jackson Immunoresearch, USA)

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Table 1. Clinical profile of patients with significant TIN in IgA nephritis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Proteinuria g/day</th>
<th>Hematuria /F</th>
<th>Cr mg/dl</th>
<th>Ccr ml/min</th>
<th>B.P. mmHg</th>
<th>B2MG1 mg/l</th>
<th>NAG2 u/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>m</td>
<td>0.5</td>
<td>many</td>
<td>1.5</td>
<td>35</td>
<td>140/90</td>
<td>7440</td>
<td>33.1</td>
</tr>
<tr>
<td>2*</td>
<td>36</td>
<td>m</td>
<td>1.8</td>
<td>5–8</td>
<td>1.2</td>
<td>85</td>
<td>150/90</td>
<td>51</td>
<td>7.5</td>
</tr>
<tr>
<td>3*</td>
<td>38</td>
<td>m</td>
<td>1.6</td>
<td>8–10</td>
<td>1.0</td>
<td>70</td>
<td>130/72</td>
<td>25</td>
<td>9.3</td>
</tr>
<tr>
<td>4*</td>
<td>15</td>
<td>m</td>
<td>1.2</td>
<td>many</td>
<td>1.0</td>
<td>95</td>
<td>105/60</td>
<td>135</td>
<td>13.3</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>f</td>
<td>2.0</td>
<td>20–30</td>
<td>1.2</td>
<td>66</td>
<td>120/70</td>
<td>128</td>
<td>20.3</td>
</tr>
<tr>
<td>6*</td>
<td>41</td>
<td>f</td>
<td>0.7</td>
<td>1–3</td>
<td>1.0</td>
<td>72</td>
<td>122/72</td>
<td>227</td>
<td>7.5</td>
</tr>
</tbody>
</table>

1 normal range, <280 2 normal range, <11.0 *with history of bacteriuria

Fig. 1. Accumulation of T lymphocytes (UCHL-1 positive) in the interstitium and around the tubules. Note preserved glomerulus without sclerosis. PAP method.

Fig. 2. Interstitial infiltration of macrophages (CD68 positive). Some are seen within the tubules. PAP method.

Fig. 3. Interstitial lesion with tubulitis. Tubular basement membrane is thickened and has become partially unclear (arrowhead). Mild sclerotic change is seen in the glomerulus. PAS stain.

Fig. 4. Tubular epithelial degeneration and exfoliation (arrowheads) due to TIN. PAS stain.

Fig. 5. Recurrence of TIN. Tubulitis is found in the regenerated, but atrophic tubules with a double tubular basement membrane (arrow-heads). Mononuclear cells are also seen in the globally sclerosed glomerulus. PAS stain.

Fig. 6. Destruction of tubules. Remnant of tubular basement membrane (arrowhead) is seen in the inflamed and mildly sclerosed interstitium. PAS stain.
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and IgG (Medical Biological Laboratory, Japan) Blocks for electron microscopy were recut and thin sections were obtained for ultrastructural analysis of the tubulointerstitial lesions.

Results

Significant TIN developing throughout the biopsy specimen was observed in 6 cases (18.8%), and their clinical profiles are summarized in Table 1.

Correlation of TIN with glomerular injuries

Acuteness and chronicity indices were compared between the cases with TIN and those without TIN. The acuteness index of the former was 1.7 and chronicity index was 3.3, showing higher indices than those without TIN (0.3 and 2.1 respectively). However, the grade of glomerular sclerosis was not always as progressed as in the cases with TIN.

Character of tubulointerstitial lesions

1. Character of infiltrating cells in the interstitium and tubules: The infiltrating cells were mostly mononuclear cells, whereas plasma cells, neutrophils and eosinophils were rare in number. Immunohistochemical study to paraffin sections disclosed that the deposition of IgA and IgG was not detected in the interstitium as well as along the tubular basement membrane.

This finding was supported by the immunofluorescent study, which disclosed the absence of significant deposition of IgG, IgA, IgM, C3, and fibrin/fibrinogen in frozen sections. The infiltrating cells in the interstitium were T lymphocytes (CD34+, UCHL-1+), B lymphocytes (CD34+, L-26+) and macrophages (CD68+). T lymphocytes and macrophages were seen to show intimate contact with the tubular basement membrane (TBM) and some were seen interlocated between tubular epithelial cells and/or in the tubular lumen (Figs. 1 and 2). Intratubular emigration of macrophages was predominant in some cases. In addition, T lymphocytes and macrophages were also found in the glomeruli, global sclerosed glomeruli and in the Bowman’s space filled with extracellular matrix. Variable interstitial fibrosis had developed in accordance with mononuclear cell infiltration.

2. Extension and progression of tubulitis: Some lymphocytes and macrophages were seen to be in intimate contact with the TBM. The TBM showed occasionally thickening and otherwise thinning, lamination, splitting and even rupture, through which emigration of mononuclear cells was observed (Figs. 3 and 7). In the tubulus, the emigrating lymphocytes and macrophages were seen interposed between the epithelial cells. Commonly, they were independent, and coexistence of lymphocytes and macrophages in the same position was rather rare (Figs. 4, 8 and 9). The tubular epithelial cells showed a decrease in microvilli and basal infoldings, atrophy and degeneration. Dark cell change, single cell necrosis and detachment were randomly observed. Atrophic and degenerative change were often observed in the epithelial cells in contact with lymphocytes and macrophages (Figs. 8 and 9).

Some macrophages showed phagocytosis of debris materials. Under these circumstances, regenerative tubuli were observed with the formation of double or triple layers of TBM (Fig. 5). In such regenerated tubuli, recurrent cellular inflammation was seen (Fig. 5). Thus, some tubuli showed complete destruction and disappearance, where a remnant of TBM was observed in the fibrotic interstitium which still exhibited inflammation (Figs. 6 and 10).

Discussion

The present study disclosed that tubulointerstitial change can occur independently, and is not a secondary phenomenon following glomerular damage. Even though the activity index was higher in cases with TIN, the tubulointestinal changes were not always correlated with the frequency of glomerulosclerosis. TIN associated with pri-
ary glomerular disease has been reported in antiglomerular basement membrane nephritis, membranous nephropathy and endocapillary glomerulonephritis, where linear deposition of immunoglobulin G was detected along the TBM [6]. TIN in IgA nephritis, however, seems to be developed not by humoral antibody deposition but by cellular immune mechanism. Interstitial accumulation of lymphocytes and macrophages and further tubular involvement in the inflammatory process resembles the tubulointerstitial events in drug-induced tubulointerstitial nephritis [8], cellular rejection in a transplanted kidney [9], and chronic pyelonephritis [10]. In such instances, cellular immunity against tubular components is suspected and similar cell components have been demonstrated to participate in TIN [11–13]. In IgA nephritis, some T cell abnormalities have been reported in addition to B cell disorders [14, 15]. Activated T cell and macrophages will accelerate the interstitial inflammation and fibrosing process. In the present study, bacteriuria had been detected in several cases, and tubular damage and its antigenic presentation could be initiated by intrarenal reflux of infected urine [10].

In comparison with the analysis of interstitial inflammation and fibrosis, that of the development of tubulitis has not been fully undertaken. In this study both lymphocytes and macrophages were seen to participate in tubular damage. Emigration into the tubulus seemed to be through the damaged TBM and during the interposition between degenerative and exfoliative process of the epithelial cells was seen to occur in the involved nephron segment. Recurrence of tubulitis was also observed in the regenerative process. Final outcome of TIN was complete destruction of the tubular structure and disappearance of the nephron in the fibrotic interstitium. Under such a situation development of “atubular glomeruli” could occur and lead to a decrease in the total renal function [16, 17]. Suppression of cellular inflammation in the acute stage will be therapeutically effective to prevent interstitial fibrosis, which is the final expression of end-stage kidney.

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Address correspondence and offprint requests to: Dr. H. Shigematsu, Department of Pathology, Shinshu University School of Medicine, Matsumoto, 390, Japan

References


**Fig. 9.** Coexistence of lymphocyte (L) and macrophage (MA) interposed in the degenerated tubular epithelium (TB) ×10,000.

**Fig. 10.** Destructed tubular structure. Remnant of tubular basement membrane is seen (arrowhead) within the infiltrating cells. Mild fibrosis (FIB) is detected. ×6,700.
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