Correlation between the alteration of glomerular extracellular matrices and the progression of glomerular injuries in patients with IgA nephropathy
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Abstract: The relationship between alterations in the intensity or distribution of extracellular components and the progression of glomerular sclerosis in patients with IgA nephropathy was evaluated. Increases of IgA, C3, laminin and/or fibronectin in the glomeruli were observed in patients in the "advanced" stage of IgA nephropathy by immunofluorescence or computer imaging analysis. It appeared that hyperproduction and/or alteration of such components might induce the morphological changes seen in the glomeruli of patients with IgA nephropathy.

Key words: extracellular matrices, immunofluorescence, computer imaging analysis, IgA nephropathy

IgA nephropathy is characterized by predominant deposition of IgA and C3 in the glomerular mesangial areas, usually detected by immunofluorescence. In the "advanced" stage of IgA nephropathy, glomerular mesangial expansion and/or circumferential interposition of the mesangial matrix has also been observed by light microscopy. The extracellular matrix of the glomerular mesangium has been found to consist of type IV collagen, laminin (LN) and fibronectin (FN) by immunohistochemical analysis(1). The purpose of this study was to evaluate the relationship between
IgA nephropathy alterations in the intensity or distribution of such components and the progression of glomerular sclerosis in patients with IgA nephropathy.

MATERIALS AND METHODS

Renal biopsy specimens were obtained from 25 patients with IgA nephropathy, including 7 repeated specimens. The histopathologic findings were classified as grade I (minimal), II (slight), III (moderate) or IV (advanced). Direct or indirect immunofluorescence was performed with 1) polyclonal rabbit antiserum to human LN (BRL), 2) mouse monoclonal antibody to FN (MBM#20), 3) polyclonal sheep antiserum to the 7S domain of human type IV collagen (Sh#496) and 4) monoclonal anti-type I collagen antibody. These antibodies and antisera were kindly provided by the Department of Pediatric Nephrology, University of Minnesota, MN, USA, and Professor Yutaka Nagai, Medical Research Institute of Tokyo Medical and Dental University, Tokyo. Renal sections were also stained with FITC-labeled antihuman IgA, IgG, IgM or C3 antiserum. Computer imaging analysis was performed as described previously (2). PAP methods were also used.

RESULTS

(1). Granular deposition of IgA and C3 was marked in the glomerular mesangial areas in patients in the moderate or advanced stage of IgA nephropathy. The deposition of IgA was marked in the subendothelial regions of the glomerular capillary walls in such patients. The intensity of IgA or C3 in the glomerular capillary walls in patients in the moderate or advanced stage was significantly increased in comparison with that in patients in the minimal or slight stage (p<0.01 and p<0.05, respectively).

(2). Marked staining of LN or type IV collagen was observed linearly
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in the glomerular capillary walls in patients in the moderate or advanced stage, and an increase in FN was observed in the glomerular mesangial areas, paramesangial matrix and subendothelial regions (Fig. 1). The intensity of LN, type IV collagen or FN in the walls in the moderate or advanced-stage patients was significantly increased in comparison with that in patients in the minimal or slight stage (p<0.01, p<0.05 and p<0.05, respectively). Although the intensity of LN, type IV collagen or FN staining was significantly decreased in the glomerular sclerotic lesions, type I collagen was observed inside or around such lesions (Table 1).

(3). In imaging analysis, the mean or total intensity of IgA or FN in glomeruli in patients in the moderate or advanced stage IgA nephropathy was not significantly increased in comparison with that in patients in the minimal or slight stage. The mean intensity of type IV collagen in the glomeruli of patients in the moderate or advanced stage of IgA nephropathy was significantly decreased in comparison with that in patients in the minimal or slight stage (p<0.025). The distribution of IgA, FN or type IV collagen in glomeruli in patients in the moderate or advanced stage of IgA nephropathy was slightly increased compared with that in patients in the minimal or slight stage of this disease. The intensity or distribution of FN or type IV collagen in glomeruli in patients with IgA nephropathy was significantly increased in comparison with that in patients with mesangial proliferative glomerulonephritis (PGN) without mesangial IgA deposition.

DISCUSSION

High levels of proteinuria are frequently observed in patients in the "advanced" stage of IgA nephropathy who have IgA deposits in the
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glomerular capillary walls. It is generally considered that type IV collagen, LN, and FN are present in the glomerular basement membrane as well as in the glomerular mesangium of normal renal tissues(1).

In this study, increases in IgA, C3, LN and FN in the subendothelial portions of the glomerular capillary walls were observed in patients in the moderate or advanced stage of IgA nephropathy by ordinary immunofluorescence. An increase in IgA or FN in the glomeruli of such patients was also detected by computer imaging analysis. Although the intensity of LN, type IV collagen or FN was markedly decreased in the sclerotic glomeruli, type I collagen was observed in such glomeruli. In the "advanced" stage of IgA nephropathy, glomerular mesangial expansion and/or circumferential mesangial interposition were observed in the glomeruli by light microscopy. It appeared that imaging analysis of glomerular extracellular components is useful for the quantitative determination of immunoglobulins and other components. It was concluded that hyperproduction and/or alteration of the glomerular extracellular components might induce the morphological changes seen in the glomeruli of patients with IgA nephropathy.

Table 1 Glomerular extracellular matrices in repeated biopsy patients with IgA nephropathy

<table>
<thead>
<tr>
<th></th>
<th>1st biopsy</th>
<th>2nd biopsy</th>
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<tbody>
<tr>
<td></td>
<td>Mesangium</td>
<td>Mesangium</td>
</tr>
<tr>
<td>IgA</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>C3</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Laminin</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Fibronectin</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Type IV collagen</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Type I collagen</td>
<td>-</td>
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</tr>
</tbody>
</table>
IgA nephropathy

Fig. 1 Staining of fibronectin (FN) in the glomerular mesangial areas and capillary walls in a patient with IgA nephropathy (x400)

REFERENCES