Multiplicity of Histopathologic Renal Lesions in IgA Nephropathy: Retrospective Analysis of Histologic Grade and Stage in Serial Biopsy Specimens

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Background: A slit system for scoring histologic grade and stage has been proposed for the evaluation of renal tissue injury in IgA nephropathy. This grade-stage system (G-S system) represents the histologic analysis of the disease state.

Methods: The first and the subsequent renal biopsy specimens were analyzed using the G-S system in periodic acid methenamine silver stained sections. The sequential change of histologic grade and stage seen in the serial sections was examined to show the natural histologic events occurring during the prolonged course of this disease.

Results: The histologic multiplicity of IgA nephropathy was simplified by subclassifying the findings into 4 groups: low active, active, active sclerosing, and sclerosing. Since the histologic grade represents activity or acuteness of the disease, and stage correlates with sclerosis, the low active group can be expected to be the major population, and the other 3 groups will include cases with more advanced IgA nephropathy.

Conclusion: The G-S system was useful for measuring the disease state of IgA nephropathy. Such a slit system is recommended to aid in the selection of therapy and the follow-up of patients.

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Key words: IgA nephropathy, grade, stage, activity, chronicity

IgA nephropathy was first reported in 1968 by Berger, and is now common throughout the world,[1–3] particularly in Japan.[4,5] Although the disease was first thought to have a benign prognosis, it is now known that approximately 40% of the cases in France progress to end-stage renal failure.[6] A similar pattern has also been observed in Japan.[7]

Concentrated analysis and investigation regarding the management and therapeutic approach to this disease are therefore required. One of the groups studying progressive renal disease from the Ministry of Health and Welfare of Japan used specimens from serial renal biopsies to retrospectively study the histopathologic progression or regression of IgA nephropathy. This study has elucidated the multiplicity of the glomerular tissue damage found in IgA nephropathy during its prolonged clinical course.

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MATERIALS AND METHODS

The first and the subsequent renal biopsy specimens from patients with IgA nephropathy were sent from 7 institutions to the Department of Pathology, Shinshu University School of Medicine, for light microscopy analysis. The specimens were stained with periodic acid Schiff and periodic acid methenamine silver (some specimens were also stained with hematoxylin and eosin). Individual tissue samples containing more than 10 glomeruli from the first renal biopsies were evaluated. The minimum interval between the succeeding biopsies was set at 6 months, as it was estimated that an acute lesion could resolve or develop postinflammatory sclerosis within this period. A total of 85 samples (from 39 male and 46 female patients) were considered to be assessable. The 85 specimens included 74 samples from the second biopsy, 9 samples from the third biopsy, 1 sample from the fourth biopsy, and 1 sample from the fifth biopsy. The interval between biopsies ranged from 6 months to 16 years, with an average of 4 years.

The histologic classification of the degree of IgA nephropathy was done by using the grading and

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staging[8,9] classification shown in Table 1. Briefly, the evaluation of histologic activity focused on the amount of acute and chronic lesions among the endocapillary, extracapillary, and interstitial lesions.

As shown in Table 1, the extent of the area of acute lesions is expressed as 1 of 4 grades. The endocapillary grade (G_{en}) ranges from 0 to 3, and the extracapillary grade (G_{ex}) ranges from 0 to 3, in each glomerulus. The chronic lesions are graded from 0 to 3 for stage of matricial increase in endocapillary (S_{en}) and extracapillary (S_{ex}) areas. The mean grade and stage for all glomeruli in the biopsy specimen is represented as G_g (0–6) and S_g (0–6). By adding the interstitial grade and stage, G_{int} (0–3) and S_{int} (0–3), total estimation of histologic renal injury is finally expressed as G (0–9) and S (0–9).

RESULTS

Subclassification of IgA Nephropathy by the Sequence of Grading and Staging

The highest values for G_g and S_g in the first renal biopsy samples were 2.3 and 3.1, respectively. Twenty-one percent of the samples from the first biopsies had a mean G_g of greater than 1. In contrast, in the subsequent biopsies, the highest G_g and S_g values were 1.4 and 5.3, respectively.

The tentative evaluation of high or low scores was based on the distribution of scores of the highest G_g and S_g values in the subsequent biopsies. Thus, the values of more than 0.5 for G_g and 3.0 for S_g were tentatively regarded as high counts. With this evaluation system, the 85 samples could be classified into 4 subgroups. In the low active group (Fig. 1), the first biopsy showed low or high values for G_g and low values for S_g, while in the subsequent biopsies, the count was low for both G_g and S_g. Fifty-four of 85 samples (63.5%) were classified in this group. The active group (Fig. 2) included the samples that showed low or high values for G_g and low values for S_g in the first biopsies, and high values for G_g but still low values for S_g in the second biopsies. Fifteen cases (17.6%) were included in this group. In the active sclerosing group (Fig. 3), the values for both G_g and S_g were high in the subsequent biopsies. Seven cases (8.2%) were found in this study. The sclerosing group (Fig. 4) showed low values for G_g, but high values for S_g, in the subsequent biopsies. Nine cases (10.5%) were classified in this group.

Glomerular Tissue Injury during Serial Biopsies

In the low active group, the value for G_g was relatively higher in the initial biopsy samples, in most cases. But in the active group, the value mostly increased by the second biopsy. After the second biopsy, additional, varying grade patterns were noted in the samples, including a change from active to low active group in 2 cases, a constant low active status in 5 cases, a constant active status in 2 cases, a change from low active to active sclerosing in 1 case, and a change from active to sclerosing in 1 case (Fig. 5). In regard to staging, even in the low active group,

Table 1. Extent of renal tissue damage, according to the grade-stage system.[a]

Variable	Index for grade (G)	Index for stage (S)
Endocapillary change	Endocapillary proliferation Mesangial reticularization Mesangiolysis Fibrin thrombi Tuft necrosis G_{en} (0–3)	Matricial increase represented in Mesangial cell proliferation Mesangial interposition Segmental sclerosis Global sclerosis Collapse S_{en} (0–3)
Extracapillary change	Exudates into urinary space Rupture of GBM Inflammatory cells Parietal epithelial proliferation Cellular crescent G_{ex} (0–3)	Matricial increase represented in Adhesion Fibrocellular crescent Fibrous crescent Pseudotubularization S_{ex} (0–3)
Glomerular grade and stage	G_g (0–6)	S_g (0–6)
Tubulointerstitial change	Edema Cell infiltration Tubulitis	Interstitial fibrosis
Interstitial grade and stage	G_{int} (0–3)	S_{int} (0–3)
Total grade and stage	G (0–9)	S (0–9)

GBM, glomerular basement membrane. [a]Based on a system proposed by Shigematsu.[8,9]

the score of S_g showed a relative increase in most cases. There was no significant correlation between S_g and S_{int}.

Participation of Interstitial Changes in IgA Nephropathy

Mononuclear cell (lymph-monocytic) infiltration (G_{int}) in the interstitium of a grade higher than 1, and sometimes with tubulitis, was found in 40 cases (47.1%) from the first biopsy. Among these 40 cases, 93% showed grade 1, and only 2 cases showed grade 2. Interstitial fibrosis (S_{int}) of stage 1 was seen in 65% of these 40 cases.

In the second biopsy, the cases showing cellular infiltration increased to 61 cases (71.8%), and among them grade 2 was seen in 7 cases (11.5%). Interstitial

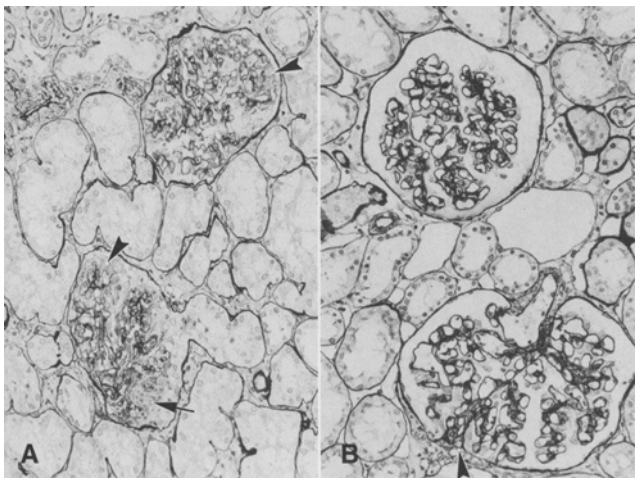

Fig. 1. A case of low active group in IgA nephropathy. (**A**) First biopsy sample showing segmental endocapillary (arrowheads) and extracapillary proliferation (arrow). At this time the mean grade and stage for all glomeruli in the sample was G_g (1.3), S_g (0.4); adding the interstitial grade and stage, the total estimation of histologic renal injury was G (2.3), and S (0.4). (**B**) Second biopsy sample, obtained 2 years and 2 months after the initial biopsy. Minor glomerular change is seen, except for the adhesive lesion at the arrowhead. G_g (0.1), S_g (1.1); G (0.1), S (1.1).

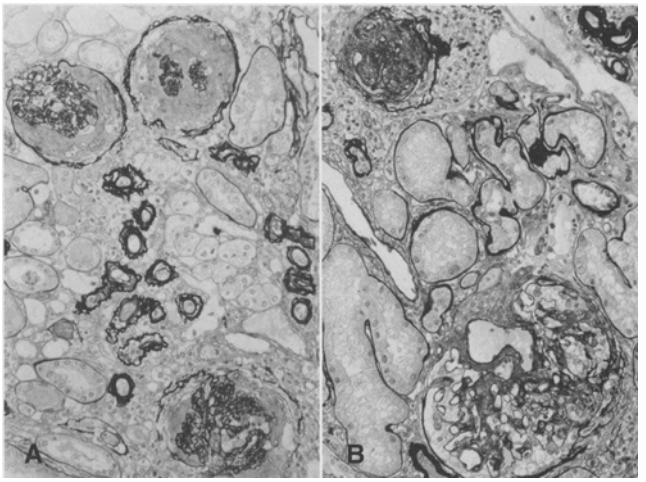

Fig. 3. A case of active sclerosing group in IgA nephropathy. (**A**) First biopsy sample showing marked cellular crescent formation with collapsed glomerular tufts. Atrophy of tubulus with cellular infiltration is observed. G_g (2.3), S_g (2.3); G (4.3), S (3.2). (**B**) Second biopsy sample, obtained 2 years and 2 months after the first biopsy. Segmental endocapillary proliferation, adhesion and pseudotubulus are seen with mesangial sclerosis at lower right of the hypertrophied glomerulus. Global sclerosis is seen at upper left of the figure. G_g (0.6), S_g (3.9); G (2.5), S (5.8)

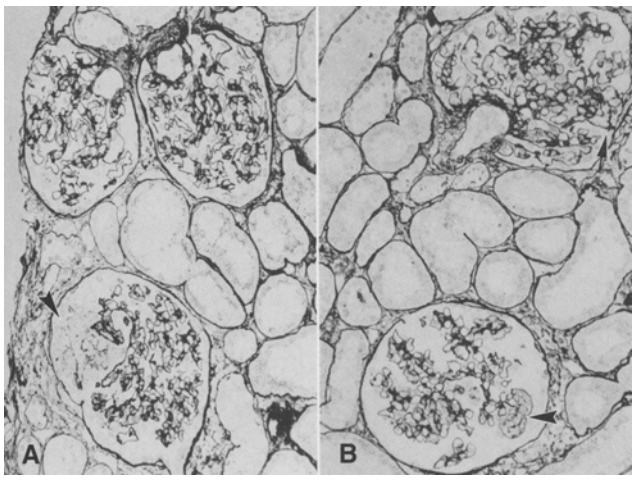

Fig. 2. A case of active group in IgA nephropathy. (**A**) First biopsy sample showing segmental extracapillary exudation with disruption of basement membrane (arrowhead). G_g (0.3), S_g (0.8); G (1.3), S (1.8). (**B**) Second biopsy sample obtained 8 months after the first biopsy. Adhesion (arrow) and endocapillary proliferation with mesangial reticularization (arrowhead). G_g (0.5), S_g (0.8); G (1.5), S (1.4)

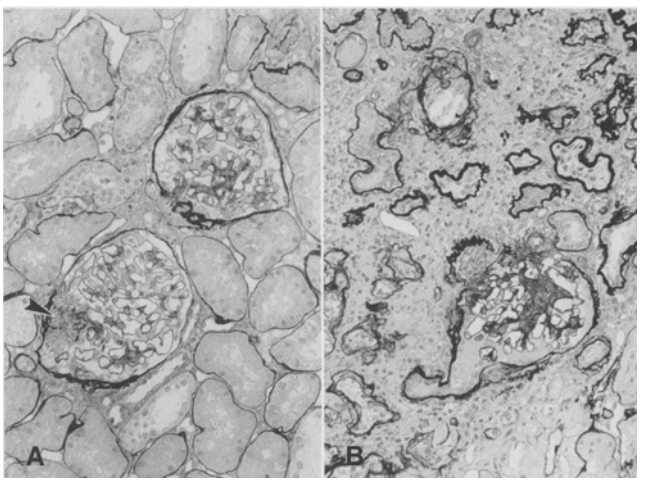

Fig. 4. A case of sclerosing group in IgA nephropathy. (**A**) First biopsy sample, showing segmental necrotizing lesion with small crescent (arrowhead). G_g (1.1), S_g (1.2); G (2.1), S (1.2). (**B**) Second biopsy sample, obtained 3 years and 2 months after the initial biopsy. Mesangial sclerosis is evident but no acute lesion. Interstitial cellular infiltration with fibrosis and tubular atrophy is observed. G_g (0), S_g (5.3); G (1), S (6.3)

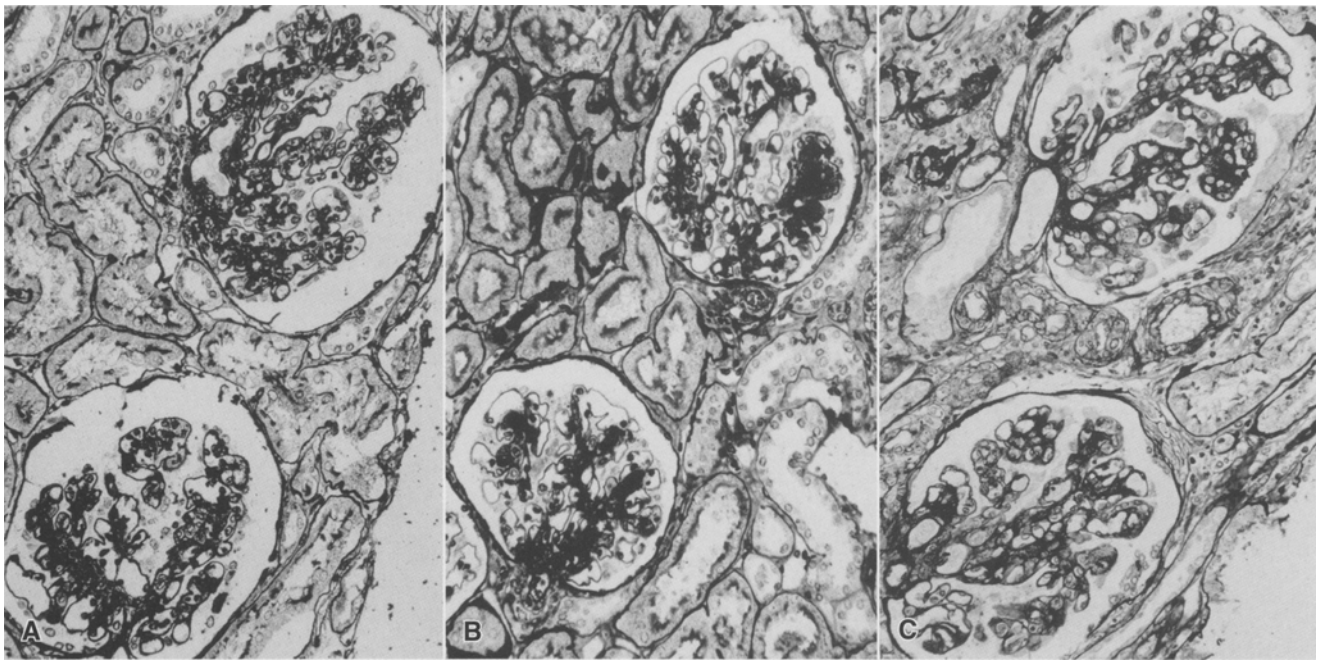

Fig. 5. A case showing changing glomerular histology during serial biopsies. (**A**) First biopsy sample, showing endocapillary proliferation. (**B**) Second biopsy sample, obtained 2 years and 5 months after the first biopsy. Axial mesangial sclerosis is dominant. (**C**) Third biopsy sample, obtained 7 years after the second biopsy. Mesangiocapillary proliferation with small crescents is seen in both glomeruli.

fibrosis was seen in most of these cases, and stage 2 fibrosis was found in 21 cases (24.7%). Six patients who had undergone hemodialysis were included among those 21 cases (28.6%), and 5 of them showed more than 3 in the S_g score.

DISCUSSION

Applying the grade-stage system (G-S system)[8,9] in serial biopsy specimens clearly shows that there may be at least 4 types of histologic progression in IgA nephropathy. The author tentatively subclassified those as low active, active, active and sclerosing, and sclerosing groups.

The majority of patients with this disease are in the low active group, and this classification may represent the most common form of this disease. Conversely, the latter 3 groups may represent patients with the most active form of the disease, since the incidence in this survey was 36%, a value closely resembling the proportion of cases of IgA nephropathy progressing to end-stage renal failure.[6,7] As previously reported,[8,9] IgA nephropathy is histologically made up of at least 3 types of tissue damage: 1) minimal inflammation with deposition, but with minor matricial increase; 2) an acute lesion characterized by matricial damage with inflammatory cell accumulation and intrinsic cell proliferation; and 3) a chronic lesion, mainly composed of postinflammatory sclerosis.

It is obvious that the low active group is characterized by minimal inflammation and deposition and, even in cases initially containing acute lesions, the tissue injury could undergo a minimal change after the resolution of acute inflammation. Acute lesions could regress, but delayed healing and/or frequent occurrence of acute inflammation could deteriorate glomerular structure with matricial increase, which is a feature of the active and active sclerosing groups. Chronic lesions are the indicator of the stage of the glomerular disease, and a high stage is associated with a high risk of chronic renal failure[10,11] particularly in the cases with a high stage of interstitial fibrosis. Thus, the participation of interstitial inflammation and fibrosis in the decrease of renal function was also reconfirmed in this study, as has been reported,[12,13] although the possibility of concomitant chronic pyelonephritis could not be ruled out.[12]

This study further elucidated that both acute and chronic lesions could appear with different degrees of tissue damage at different intervals during the prolonged clinical course of this disease. Although the histologic analysis of the first biopsy is informative for the selection of therapy in IgA nephropathy,[14] there may be little predictive information in this specimen concerning the patient's prognosis.

Recently, histologic subclassification of IgA nephropathy was proposed[15] where 5 groups, minimal histologic lesion, focal-segmental glomerulosclerosis-like, focal proliferative glomerulonephritis, diffuse proliferative glomerulonephritis, and advanced chronic glomerulonephritis, were subclassified as subclass I to subclass V. The greatest survival was found in subclass I and II, followed by III, IV, and V. Such a pathologic grouping (grouping pathologic

characteristics or lumped system[19]) is simple and easy to apply, but is weak in flexibility of interpretation, that is, it is easy to miss important isolated pathologic changes. As became evident in the present analysis, in serial biopsy specimens the histology of IgA nephropathy could change and thus there is no assurance that the one histologic pattern will continue throughout the clinical course in any given patient with IgA nephropathy.

In contrast, histologic application of grade and stage is a slit system, and obviously adds significant complexity to the analysis. But the system is valuable in the analysis of acuteness and chronicity of the disease and in the evaluation of the effect of treatment, as shown in several studies.[16–18]

For the development of a comprehensive system for the identification and follow-up of patients with IgA nephropathy, a group of renal pathologists and nephrologists in the United States discussed the development of a regional data bank for this disease and published a report on management of biopsy data for IgA nephropathy.[19] In evaluation of renal pathology in biopsy specimens, this Memphis system introduced a slit system, and recommends the scoring of every item in light, immunofluorescent, and electron microscopy. Although there is no definite evaluation of grade and stage, one can gain the information about the acuteness and chronicity of the disease from this data bank. Thus slit systems, including the G-S system, seem to be rational methods for selecting treatment and evaluating follow-up care for the patients with IgA nephropathy.

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