Clinical Significance of the Intensity of Glomerular Galactose-Deficient IgA1 Deposition in IgA Nephropathy

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INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerular disease.1 IgAN has a poor prognosis because 20% to 40% of patients develop end-stage kidney disease within 20 years. Immunofluorescence staining demonstrates IgA and complement (C)-3 deposits predominantly in the glomerular mesangial region, and other immunoglobulins, such as IgG and IgM, are also often deposited in the glomerulus.2 Previous studies have reported a relationship between the immunofluorescence findings and clinical or pathological features.3–7 The intensity of glomerular IgA deposition did not correlate with the degree of histopathological severity.4 In contrast, the presence of IgG deposition was significantly associated with the mesangial and endocapillary proliferation.8 Heybeli et al.9 investigated the clinical relevance of IgM deposition in patients with IgAN and its impact on renal survival.9–10 IgM deposition had more severe proteinuria and poorer renal function.

There is increasing evidence that galactose-deficient IgA1 (Gd-IgA1) is increased in the serum of patients with IgAN.4,11 Glomerular Gd-IgA1 was specifically deposited in patients with IgAN by using the Gd-IgA1 monoclonal antibody (KM55 monoclonal antibody).12–13 Immunostaining using the Gd-IgA1 monoclonal antibody may provide useful clues to distinguishing between the primary and secondary IgAN.14–16 However, there are only a few reports on the clinical importance of Gd-IgA1 deposition in the pathogenesis of IgAN. Therefore, we investigated the relationship between Gd-IgA1 deposition and clinicopathological parameters in patients with IgAN.

RESULTS

Patient Characteristics

Globular Gd-IgA1 deposition was positive in all patients with IgAN, and the average Gd-IgA1 deposition area was 6.99 ± 4.60%. We divided the patients into tertiles according to the Gd-IgA1 deposition area as follows: low-intensity group (n = 47), 0.48% to 3.85%; medium-intensity group (n = 47), 3.92% to 8.13%; high-intensity group (n = 47), 8.31% to 22.82% (Supplementary Figure S1).

High-intensity Group Shows Higher Levels of Proteinuria and Urinary Gd-IgA1

The patients’ clinical characteristics are presented in Supplementary Table S1. There was no correlation between the intensity of Gd-IgA1 deposition and age or serum creatinine, IgA, C3, and Gd-IgA1 levels. Proteinuria was significantly higher in the high-intensity group than in the other 2 groups. There was no significant difference in the serum Gd-IgA1 levels among the 3 groups; however, urinary Gd-IgA1 levels in the high-intensity group were significantly higher than those in the medium-intensity group (P < 0.05, Figure 1).

Treatment Information

None of the patients were treated with steroids or immunosuppressive drugs before renal biopsy. Renin-angiotensin system inhibitors were taken by 11 patients (23.4%) in the low-intensity group, 7 (14.9%) in the medium-intensity group, and 8 (17.0%) in the high-intensity group. There was no significant
difference in renin-angiotensin system inhibitor usage between the groups.

**Histological Acute Lesions Correlated With the Intensity of Glomerular Gd-IgA1 Deposition**

There was significantly more proteinuria and glomeruli with acute lesions among the IgM-positive patients than the IgM-negative patients (Supplementary Figure S2a and S2b). Patients with IgG deposition demonstrated a significantly higher percentage of glomeruli with acute lesions (Supplementary Figure S2c).

A total of 37 patients had histological acute lesions, with 6 patients in the low-intensity group, 15 in the medium-intensity group, and 16 in the high-intensity group. The average percentages of glomeruli with acute lesions to total glomerular count were 0.4%, 1.4%, and 2.1% in the low-intensity, medium-intensity, high-intensity groups, respectively. The percentage of acute lesions was significantly higher in the high-intensity group, whereas the percentage of chronic lesions did not differ between the groups (Figure 2). Findings revealed no difference in the intensity of IgA deposition or the presence of IgG deposition between the groups. C3 deposition tended to be stronger in the high-intensity group, whereas IgM deposition was more prevalent in the medium-intensity and high-intensity groups (Supplementary Figure S3). The percentages of E1 and C1 in the Oxford classification increased in patients of the high-intensity group. However, there was no difference in the percentages of M1, S1, or T1 among the groups (Supplementary Figure S4).

**DISCUSSION**

In this study, we observed that the intensity of Gd-IgA1 deposition is related to the acute lesion of IgAN. It has been reported that the degree of proteinuria is an important factor in the progression of
IgAN or chronic kidney disease.\textsuperscript{17–19} We have previously reported that urinary Gd-IgA1 levels correlated with proteinuria.\textsuperscript{6} In the present study, we observed that the stronger the glomerular Gd-IgA1 deposition, the higher the level of proteinuria and urinary Gd-IgA1, which is consistent with previous reports. However, there was no correlation between the serum Gd-IgA1 levels and intensity of glomerular Gd-IgA1 deposition in our study. Currently, a multihit hypothesis is considered to explain the pathogenesis of IgAN as follows: production of Gd-IgA1 (Hit 1), production of Gd-IgA1-specific antibodies (Hit 2), formation of immune complexes (Hit 3), deposition in mesangial regions (Hit 4), and induction of tissue damage.\textsuperscript{7} Bagchi et al.\textsuperscript{8} reported that there was no correlation between serum Gd-IgA1 and histological severity. Thus, the serum Gd-IgA1 only cannot explain the pathogenesis of IgAN. In the present study, glomerular Gd-IgA1, which is associated with histological acute lesion does not correlation with serum level of Gd-IgA1.

The stronger the glomerular Gd-IgA1 deposition, the greater the IgM deposition. Takahata et al. reported that the apoptosis inhibitor of macrophage protein forms IgG/IgM immune complexes and is involved in the progression of nephritis after glomerular IgA deposition in the glomeruli, as observed in spontaneous IgAN model mice. apoptosis inhibitor of macrophages were also observed to be codeposited with IgA and IgG/IgM in the glomeruli of patients with IgAN.\textsuperscript{9} Therefore, it was suggested that Gd-IgA1 might be one of the factors regulating the amount of IgG/IgM immune complexes and thus the subsequent degree of complement activation.

In the Oxford classification, mesangial hypercellularity, segmental glomerulosclerosis, tubular atrophy or interstitial fibrosis, and crescents are considered as those lesions that affect the renal prognosis, and endocapillary hypercellularity has been described as a lesion that responds to immunosuppressive drugs.\textsuperscript{20} In the Japanese histological severity classification, cellular or fibrocellular crescents are identified as acute lesions that are subjected to immunosuppressive treatment, whereas global, segmental sclerosis and fibrous crescents are identified as chronic lesions that are related to dialysis induction.\textsuperscript{21} The common histological prognostic factors for both classifications were segmental glomerulosclerosis and crescents. Furthermore, previous studies have reported that the degree of mesangial deposition of Gd-IgA1 correlated with renal damage in IgAN.\textsuperscript{5} The present study found that there were significantly more active lesions, such as endocapillary hypercellularity and cellular or fibrocellular crescents in the high-intensity group, which may reflect the disease activity.

This study has several limitations. First, the data were obtained from a single institution. Second, we only analyzed data from a renal biopsy; therefore, we do not know whether glomerular Gd-IgA1 deposition is an indicator of treatment response or a factor affecting the renal prognosis. In the future, it is necessary to analyze the relationship between the follow-up data and renal outcomes.

In conclusion, glomerular Gd-IgA1 deposition may be a useful index for therapeutic interventions, because the intensity of deposition correlates with the disease activity.

**DISCLOSURE**

All the authors declared they have no competing interests.

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**AUTHOR CONTRIBUTIONS**

MN, HS, and YS designed this study. MN, YF, and TK conducted the experiments. MN analyzed the data. MN,
HS, and YS drafted the manuscript. All authors have read and approved the final draft of the manuscript.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Three groups divided by intensity of glomerular Gd-IgA1 deposition.

Figure S2. Association between IgM/IgG deposition and clinical features.

Figure S3. IgM deposition was more prevalent in the middle and high intensity groups.

Figure S4. The percentages of E1 and C1 in the Oxford classification increased in patients of the high-intensity group.

Table S1. Clinical characteristics of patients with IgA nephropathy at the time of renal biopsy.

Table S2. Association of intensity of glomerular Gd-IgA1 with treatment and clinical outcome.

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