

Renal Outcome of Immunoglobulin A Nephropathy with Mild Proteinuria

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We determined the natural history of immunoglobulin A nephropathy (IgAN) among patients who presented with mild proteinuria (0.2 to 0.4 g/day), and factors associated with development of adverse clinical events, defined as proteinuria ≥ 1.0 g/day, blood pressure $> 130/80$ mmHg, serum creatinine ≥ 1.4 mg/dl. We did analyzed data from 27 patients (mean age 30 ± 12 years) with IgAN accompanied by mild proteinuria between 1990 and 1998. We also evaluated semiquantitative scores of glomerulosclerosis, tubulointerstitial injury, hyaline arteriosclerosis, and IgAN classification. The median duration of follow-up was 51 months. During follow-up, at least one adverse clinical event affected 15 patients (56%): among who eight (53%) developed proteinuria. And one of 8 developed impaired renal function and 7 (47%) became hypertensive. Another 12 patients (44%) were not affected by adverse clinical events. The clinical findings were not significantly different between the adverse events and no events group. The scores of glomerulosclerosis and tubulointerstitial injury revealed significant differences between events. The only renal histological parameters of glomerulosclerosis and adverse clinical events were statistically correlated with renal survival. We concluded that IgAN with mild proteinuria frequently follows a slow by progressive course and that the severity of glomerulosclerosis may be predictable prognostic factor in patients who have IgAN with by mild proteinuria.

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Introduction

Immunoglobulin A nephropathy (IgAN) is the most widespread primary glomerulonephritis worldwide and particularly in Japan [1,2]. This condition is one of the most important causes of end-stage renal disease (ESRD), which develops in up to 40% of patients who have had IgAN for 20 years [3-5]. Advanced age, hypertension, proteinuria, and renal impairment at presentation are poor prognostic indicators, but patients who present with isolated macroscopic or microscopic hematuria, are generally believed to have better a prognosis [5,6]. Most observations of the natural history of IgAN involve heterogeneous groups of patients with many different clinical permutations [8-10]. Recently, we reported that IgAN with proteinuria (0.5 to 1.0 g/day) was slow progressive at the outpatient clinic [7]. Moreover, the severity of glomerulosclerosis may be the important prognostic factor in IgAN with proteinuria at the time of the initial biopsy [7]. The purpose of the present study is to determine the prognosis of IgAN with mild proteinuria (0.2 to 0.4 g/day), we analyzed renal biopsied specimens and clinical data from the outpatient clinic.

Patients and Methods

Patient Selection and Clinical Investigation

We reviewed all patients who were diagnosed with IgAN from biopsy specimens at Nagasaki Municipal Medical Center (Nagasaki, Japan) during the period from 1990 to 1998. Primary IgAN were selected based upon four sets of criterias follows. 1) A diagnosis of IgAN based on predominant immune complexes containing mesangial IgA detected by immunofluorescence in ultrastructures, irrespective of light microscopic

features; the intensity of immunofluorescence for IgA and C3 had to be at least 1+ on a scale of 3+. Patients with systemic diseases such as diabetes, lupus erythematosus, chronic liver diseases, renal allografts, and Henoch-Schonlein purpura were excluded. 2) A serum creatinine level below 1.3 mg/dl, an estimated 24-hour urinary creatinine clearance according to the Gault-Cockcroft equation [8] of over 100 ml/min per 1.73 m² of body surface area, proteinuria of 0.2 to 0.4 g per day, and no signs of hypertension at the time of renal biopsy. 3) At least 6 glomeruli [9], 5 mm of cortex, and three arterioles were required in light microscopic sections. Records of 110 patients who fulfilled these criteria were reviewed and analyzed for age, sex, follow-up period, serial serum creatinine levels, proteinuria, blood pressure, and renal outcome. 4) A minimum of 12 months of outpatient follow-up finally selected 27 patients.

Follow up for Adverse Clinical Events

We reviewed the clinical records of the remaining 27 patients during treated with antiplatelet agents only. Adverse clinical events included proteinuria \geq 1.0 g per day on two consecutive occasions; development of hypertension, (systolic blood pressure > 130 mmHg or diastolic blood pressure > 80 mmHg) and a need for antihypertensive therapy; impaired renal function when serum creatinine levels increased to 1.4 mg/dl or greater, or an estimated 24-hour urinary creatinine clearance of < 70 ml/min per 1.73 m² of body surface.

Renal Pathological Evaluation

Sections of biopsy specimens were stained with periodic acid-Schiff's reagent, periodic acid-Schiff-methenamine silver or Masson-trichrome. All renal biopsy specimens were reviewed by two investigators (Y.H., and T.T.) unaware of the patient's clinical condition in a double-blind examination of the same slides. We graded renal biopsy specimens as described [10] and semiquantified the severity of glomerulosclerosis [11], tubulointerstitial damage, and hyaline arteriosclerosis [12]. The ratio (%) of glomerulosclerosis was determined after excluding glomeruli located within areas of subcapsular scar. The summarized grading scores were as follows.

Classification of IgAN. Grade 1, minor change; Grade 2, segmental mild proliferation; Grade 3, segmental moderate or global mild proliferation; Grade 4, global moderate proliferation and Grade 5, global severe proliferation. The grade was calculated as the mean value for the degree of mesangial proliferation for all glomeruli evaluated (Figure 1). Glomerulosclerotic scores (GS): 0, no sclerosis; 1, sclerosis of 25% or less; 2, sclerosis of 26% to 50%; 3, sclerosis of 51% to 75%; 4,

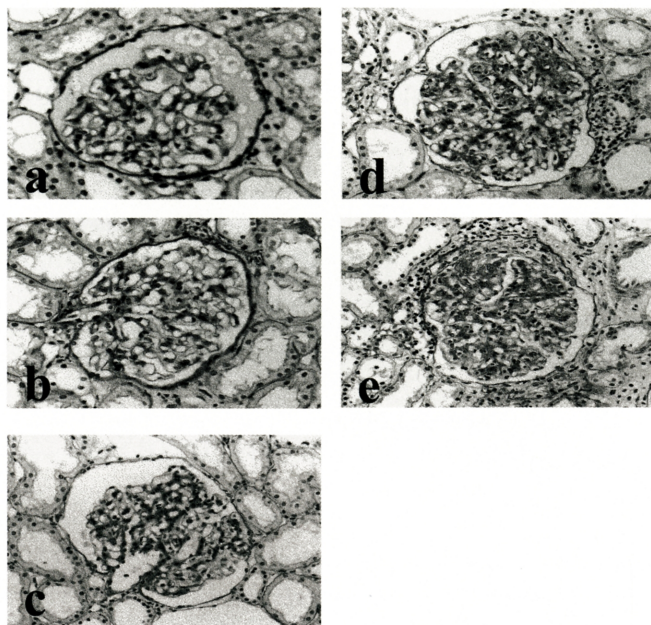


Figure 1. Classification of immunoglobulin A nephropathy. a: Grade 1, minor change; b: Grade 2, segmental mild proliferation; c: Grade 3, segmental moderate or global mild proliferation; d: Grade 4, global moderate proliferation; e: Grade 5, global severe proliferation. Periodic acid-Schiff; original magnification x 150.

sclerosis of 76% to 100%.

Tubulointerstitial score (TIS). The areas of tubular atrophy and interstitial fibrosis in the renal cortex, regardless of inflammatory cells, were estimated in ratios (%) and graded as follows: Grade 0, tubular atrophy and interstitial fibrosis were absent or less than 5%; Grade 1, 5% to 49%; and Grade 2, 50% or greater (Figure 2).

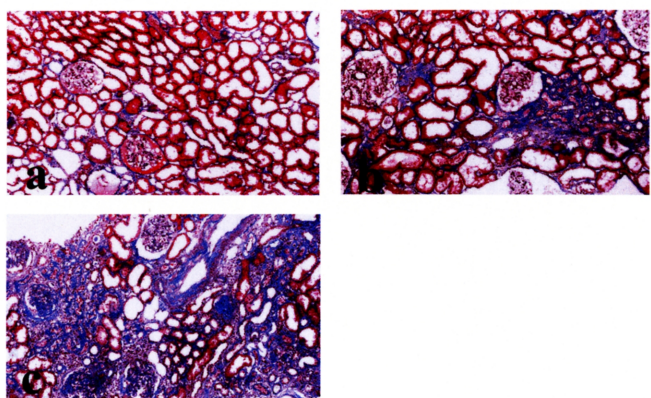


Figure 2. Tubulointerstitial score. The areas of tubular atrophy and interstitial fibrosis in the renal cortex, regardless of inflammatory cells, were estimated in ratios (%). a: Grade 0, tubular atrophy and interstitial fibrosis were absent or less than 5%; b: Grade 1, 5% to 49%; c: Grade 2, 50% or greater. Masson-trichrome; original magnification x 120.

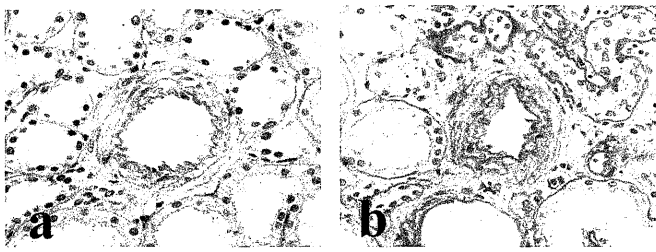


Figure 3. Hyaline arteriosclerosis. a: Grade 1, present; b: Grade 0, absent. Periodic acid-Schiff; original magnification x 200.

Hyaline arteriosclerosis (HA) was recorded as Grade 1, present or Grade 0, absent (Figure 3).

Statistical Analysis

All statistical analyses were performed using Statview 5.0 for Windows software (SAS Institute Inc., Cary, USA). Results are expressed as means \pm SD unless otherwise stated. Statistical significance was examined using the Mann-Whitney *U* test with the Bonferroni correction. The incidence of adverse events was estimated using the Kaplan-Meier method and compared using the log rank test. Multivariate analysis was not performed because of the relatively small number of selected patients. Variables included age at presentation, sex, serum IgA level, presence of macroscopic hematuria, presence of detectable proteinuria (0.2 to 0.4 g/day) at presentation, and the histologic grade of the renal biopsy specimen. A *P* value below 0.05 was considered statistically significant.

Results

The mean age of the 14 male and 13 female patients at presentation was 30 ± 12 years (range 16 to 62). At presentation, 7 patients (26%) had elevated serum IgA concentrations (110 to 410 mg/dl) and none of the 27 had low serum complement levels. The median follow-up was 51 months (range 12 to 137), during which, 15 patients (56%) developed at least one adverse event (events group). 8 of these patients (53%) developed proteinuria and 3 of those 8 had hypertension. And that one developed impaired renal function that progressed to ESRD 60 months after initial presentation and 7 (47%) became hypertensive. Another 12 patients (44%) had persistent abnormalities in urinalysis examinations, without development of adverse events (no events group). Adverse events developed within a median of 41 months (range 6 to 126). The clinical findings were not significantly different between the two groups (Table 1). We summarized pathological

Table 1. Clinical characteristics at the time of presentation in events and no events groups

	Events group (n = 15)	No events group (n = 12)	<i>P</i> value
Age (years)	38 \pm 12	24 \pm 5	0.06
Gender (M/F)	9/6	5/7	0.34
Duration time (month)	44 \pm 32	59 \pm 32	0.07
Body mass index (kg/mm ²)	23.3 \pm 2.8	22.8 \pm 3.3	0.90
Serum creatinine (mg/dl)	0.9 \pm 0.2	0.8 \pm 0.2	0.31
Urine creatinine (mg/dl)	110 \pm 67	93 \pm 40	0.37
Creatinine clearance (ml/min)	115 \pm 15	122 \pm 20	0.30
Serim Immunoglobulon A (mg/dl)	359 \pm 114	344 \pm 129	0.40
Fibrinogen	263 \pm 48	249 \pm 77	0.83
Serum complement titer (U/ml)	36.8 \pm 2.9	36.2 \pm 4.3	0.78
Uric acid (mg/dl)	5.9 \pm 1.2	5.4 \pm 1.1	0.60
Macrohematuria	1/15	4/12	0.08

Value expressed as mean \pm SD. n: number of patients

Table 2. Comparison of renal histopathologic findings in immunoglobulin A nephropathy in patients with events and those with no events groups

	Events group (n = 15)	No events group (n = 12)	<i>P</i> value
Classification of IgAN	3.16 \pm 0.98	2.83 \pm 1.14	0.62
Glomerulosclerotic score (GS)	0.83 \pm 0.79	0.17 \pm 0.37	0.02
Tubulointerstitial score (TIS)	2.25 \pm 0.72	1.33 \pm 0.62	0.01
Hyaline arteriosclerosis (HA)	0.17 \pm 0.37	0.75 \pm 0.37	0.14

Value expressed as mean \pm SD. n: number of patients

changes in renal biopsy specimens from the 27 patients (Table 2). The Glomerulosclerotic score (GS) and Tubulointerstitial score (TIS) showed significant differences between the groups (*P* = 0.02 and *P* = 0.01, respectively), but the hyaline arteriosclerosis (HA), classifications of IgAN were not significantly different. However, although renal survival rates until development of adverse clinical events did not significantly differ from TIS, HA and Classification of IgAN (Figure 5-7), it was significantly higher when GS were low (*P* < 0.01) (Figure 4).

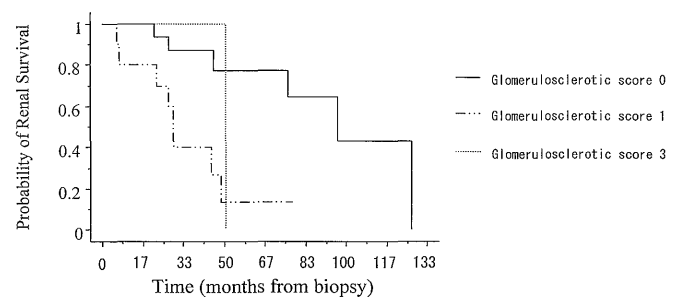


Figure 4. Renal survival rates in with mild proteinuria (0.2 to 0.4 g per day) assessed by glomerulosclerotic score. Survival rates were significantly higher when glomerulosclerotic scores were low (*P* < 0.01).

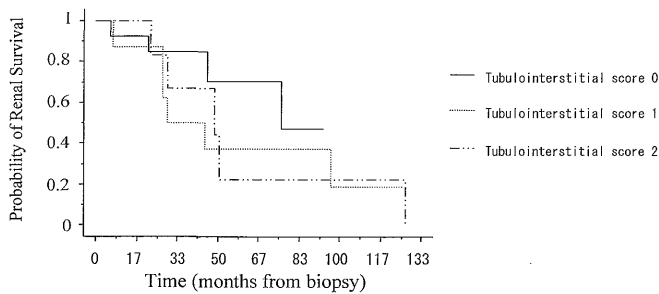


Figure 5. Renal survival rates in immunoglobulin A nephropathy with mild proteinuria assessed by tubulointerstitial score. Survival rates did not significantly differ ($P = 0.47$).

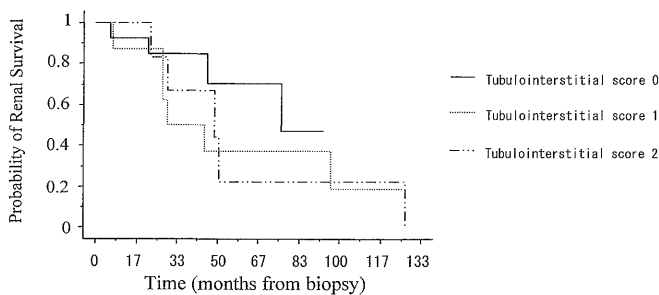


Figure 6. Renal survival rates in immunoglobulin A nephropathy with mild proteinuria with hyaline arteriosclerosis. Survival rates were not significantly affected ($P = 0.54$).

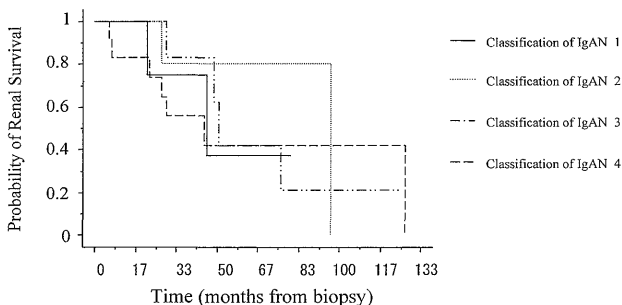


Figure 7. Renal survival rates in immunoglobulin A nephropathy with mild proteinuria according to classification. Survival rates did not significantly differ ($P = 0.87$).

Discussion

In this study, we examined the natural history of IgAN among patients who presented with mild proteinuria (0.2 to 0.4 g/day) during treated with antiplatelet agents only. Among these, over 56% of them developed proteinuria, hypertension, or impaired renal function during the follow up median of 51 months. The severity of glomerulosclerosis and tubulointerstitial injury significantly correlated with adverse clinical events including

subsequent proteinuria, hypertension, and impaired renal function. The only renal histological parameters of glomerulosclerosis and adverse clinical events were statistically correlated with renal survival. Clarkson et al. [13] reported that a tendency to progression was suggested by the presence of glomerulosclerosis. Moreover, To et al. [14] suggested that although the severity of glomerulosclerosis was the only morphological parameter that independently correlated with renal survival in adult patients with IgAN when the renal pathological characteristics of individual patients are assessed in clinical practice, information about tubulointerstitial injury and hyaline arteriosclerosis may be useful. Therefore, we postulate that glomerulosclerosis may determine the prognosis of IgAN with mild proteinuria.

Although many grading systems have correlated histological lesions with the clinical outcome of IgAN, none of them have prevailed because of several limitations, and independent prognostic significance has not been shown for any of them [15-20]. One of the major limitations is the complexity of a grading system related to the inclusion of both acute and chronic lesions. Thus, the potential importance of chronicity indices may be masked. The importance of chronic lesions and of assessing glomerular and tubulointerstitial damage in the appraisal of IgAN has been reported [10,18-21]. We therefore exclusively focused on chronic irreversible lesions and used a chronicity-based histological grading system that assessed GS, TIS, and HA over a long-term follow-up. We believe that this scoring system is convenient, simple to understand as a prognosticator in IgAN and inter and intra observer findings closely match. Our methods to determine prognostic factor in IgAN will need evaluating in a larger patients with IgAN.

Only one patient in the study group developed impaired renal function, and this progressed to ESRD 60 months after initial presentation. Impaired renal function in patients with IgAN is always preceded by the development of proteinuria followed by hypertension [22]. The practical implication is that regular monitoring of blood pressure and proteinuria are the two most important steps to identify patients at risk of deterioration [22]. We found that mild proteinuria at presentation was an indicator of adverse events: 8 (53%) developed proteinuria and 7 (47%) became hypertensive during follow up. These results suggest that mild proteinuria is one marker of IgAN progression.

We concluded that IgAN with mild proteinuria frequently follows a slowly progressive course and that the severity of glomerulosclerosis may be predictable prognostic factor for IgAN with by mild proteinuria at the time of the initial biopsy.

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References

1. Kobayashi Y, Tateno S, Hiki Y, *et al*: IgA nephropathy: Prognostic significance of proteinuria and histological alteration. *Nephron* 34: 146-153, 1983
2. Chida Y, Tomura S, Takeuchi J: Renal survival rate of IgA nephropathy. *Nephron* 40: 189-194, 1985
3. Chauvear D, Droz D: Follow-up evaluation of the first patients with IgA nephropathy described at Necker Hospital, the 25th year. *Contrib Nephrol* 104: 1-5, 1993
4. Koyama A, Igarashi M, Kobayashi M, the Research Group on Progressive Renal Diseases: Natural history and risk factors for immunoglobulin A nephropathy in Japan. *Am J Kidney Dis* 29: 526-532, 1997
5. Galla JH: IgA nephropathy. *Kidney Int* 47: 377-387, 1995
6. D'Anico G, Ragni A, Gandini E, *et al*: Typical and atypical natural history of IgA nephropathy. *Contrib Nephrol* 104: 6-13, 1993
7. Horita Y, Tadokoro M, Suyama N, *et al*: Severity of glomerulosclerosis predicts prognosis of IgA nephropathy with proteinuria. *Acta Med Nagasaki* 47: 123-126, 2002
8. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31-41, 1976
9. Pirani C: Evaluation of kidney biopsy specimens. In *Renal Pathology* (Tisher CC, Brenner BM eds.: J.B. Lippincott Company, Philadelphia) pp.85-115, 1994
10. Shimada H, Imai N, Miyakawa Y, *et al*: A clinicopathological study of adult Japanese IgA nephropathy patients: early stage cases and cases with exacerbation. *Nephrology* 3: S701-S707, 1997
11. Horita Y, Inenaga T, Nakahama H, *et al*: Cause of residual hypertension after adrenalectomy in patients with primary aldosteronism. *Am J Kidney Dis* 37: 884-889, 2001
12. Konishi Y, Imanishi M, Okamura M, *et al*: Relationship of renal histological damage to glomerular hypertension in patients with immunoglobulin A nephropathy. *J Hypertens* 18: 103-109, 2000
13. Clarkson AR, Seymour AE, Thompson AJ, *et al*: IgA nephropathy: A syndrome of uniform morphology, diverse clinical features and uncertain prognosis. *Clin Nephrol* 459-471, 1977
14. To KF, Choi PCL, Szeto CC, *et al*: Outcome of IgA nephropathy in adults graded by chronic histological lesions. *Am J Kidney Dis* 35: 392-400, 2000
15. Lee SMK, Rao VM, Franklin WA, *et al*: IgA nephropathy: Morphologic predictors of progressive renal disease. *Hum Pathol* 13: 314-322, 1982
16. Bogenschutz O, Bohle A, Batz C, *et al*: IgA nephritis: On the importance of morphological and clinical parameters in the long-term prognosis of 239 patients. *Am J Nephrol* 10: 137-147, 1990
17. Alamartine E, Sabatier JC, Guerin C, *et al*: Prognostic factors in mesangial IgA glomerulonephritis: An extensive study with univariate and multivariate analysis. *Am J Kidney Dis* 18: 12-19, 1991
18. Nieuwhof C, Kruytzer M, Frederiks P, *et al*: Chronicity index and mesangial IgG deposition are risk factors for hypertension and renal failure in early IgA nephropathy. *Am J Kidney Dis* 31: 962-970, 1998
19. D'Amico G: Influence of clinical and histological features on actuarial renal survival in adult patients with idiopathic IgA nephropathy, membranous nephropathy, and membranoproliferative glomerulonephritis: Survey of the recent literature. *Am J Kidney Dis* 20: 315-323, 1992
20. Wyatt RJ, Emancipator SN, Kon V, *et al*: IgA nephropathy database: Development of a system for management of renal biopsy acquired data. *Am J Kidney Dis* 29: 817-828, 1997
21. Lee SMK: Prognostic indicators of progressive renal disease in IgA nephropathy: Emergence of a new histologic grading system. *Am J Kidney Dis* 29: 953-958, 1997
22. Szeto C, Lai FM, To KF, *et al*: The natural history of immunoglobulin A nephropathy among patients with hematuria and minimal proteinuria. *Am J Med* 110: 434-437, 2001