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Severity of Glomerulosclerosis Predicts Prognosis of IgA Nephropathy with Proteinuria

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We determined the natural history of IgA nephropathy (IgAN) among patients who presented with proteinuria, and factors associated with the development of clinical events, namely blood pressure (BP) ≥ 130/85 mmHg, serum creatinine ≥ 1.4 mg/dl. We analyzed data from 16 patients (mean age 35 ± 14 years) with IgAN accompanied by proteinuria between 1990 and 1998. We also semiquantified scores of glomerulosclerosis (GS), tubulointerstitial damage (TID), hyaline arteriosclerosis (HA), and IgAN classification. The median duration of follow-up was 48 months. During clinical follow-up, seven (44%) patients became hypertensive, among who five (31%) developed impaired renal function and two (13%) progressed to treatment with hemodialysis. Events did not develop in the other 9 patients (56%). Clinical findings were not significantly different between the events and event-free groups. The GS and TID scores revealed significant differences between patient groups. Only the renal histological parameters of GS and events were statistically correlated with renal survival. We conclude that the severity of GS may be the important prognostic factor in patients with IgAN accompanied by proteinuria at the time of the initial biopsy.

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Key words: IgA nephropathy, proteinuria, glomerulosclerosis, hypertension

Introduction

IgA nephropathy (IgAN) is the most prevalent type of primary glomerulonephritis worldwide and in Japan[1-5]. The natural history of the disease remains controversial, but the incidence of end-stage renal disease (ESRD), whether mild, moderate, or severe, ranges from 30% to 40% within 20 years of evaluation[6-8]. However, predicting the long-term prognosis and more precisely, the subsequent development of ESRD, at the time of diagnosis remains difficult. Studies have shown that arterialthat arterial hypertension, proteinuria of over 1 g per day and the severity of histological lesions on initial renal biopsy specimens are risk factors that predict impairedpredict impaired renal function[9-12]. And hypertension is a well-documented risk factor for the progression of IgAN[13,14]. Furthermore, many clinical studies have provided evidence that antihypertensive therapy prevents the progression of renal insufficiency[15-17]. The purpose of the present study is to determine the IgAN among patients who presented with proteinuria less than 1 g per day, and clinical events such as hypertension, renal function, and pathological data at initial renal biopsy, and subsequent renal insufficiency and ESRD during follow-up.

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Patients and Methods

Patients

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. Patients with systemic diseases such as diabetes, lupus erythematosus, chronic liver diseases, renal allografts and Henoch-Schonlein purpura were excluded. Patients were selected when the serum creatinine level below was 1.3 mg/dl, estimated 24-hour urinary creatinine clearance by the Gault-Cockroft equation[18] was over 90ml/min per 1.73m^2 body surface area, proteinuria was 0.5 to 1.0 g per day and signs of hypertension at the time of the initial renal biopsy were absent. At least 6 glomeruli[19], 5 mm of cortex, and three arterioles were required in light microscopic sections. We analyzed records from 110 patients and selected 16 patients who met these criteria with a minimum of 12 months of outpatient follow-up according to age, sex, follow-up period, serial serum creatinine levels, proteinuria, blood pressure and renal outcome.

We reviewed the clinical records of these 16 patients. Clinical follow-up and events included the development of hypertension, (systolic blood pressure of $\geq$ 130 mmHg or diastolic blood pressure of $\geq$ 85 mmHg) and a need for antihypertensive therapy, defined as 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 m^2 of body surface.

Morphologic examination

Mesangial proliferation and the degree of sclerosis and/or hyalinosis of arterioles and interlobular arteries were evaluated using semiquantitative methods in all renal biopsy specimens. The percentage of sclerosed glomeruli was also determined. The degree of mesangial proliferation was determined for each glomerulus using a 5 grades according to the method by previous reported[20]. Histologic subclassification 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. The score of glomerulosclerosis (GS) was defined as the percentage of sclerotic glomeruli divided by the total number of glomeruli: 0, none; 1, sclerosis of 25% or less; 2, sclerosis of 26% to 50%; 3, sclerosis of 51% to 75%; 4, sclerosis of 76% to 100%[21]. Tubulointerstitial damage (TID). Areas of tubular atrophy and interstitial fibrosis in the renal cortex, regardless of inflammatory cells, were estimated as ratios (%) and graded as follows: Grade 0, tubular atrophy and interstitial fibrosis were absent or less than 5%; 1, 5% to 49%; and 2, 50% or greater[22]. Hyaline arteriosclerosis (HA) was graded as 1, present or 0, absent[22] (Figure 1).

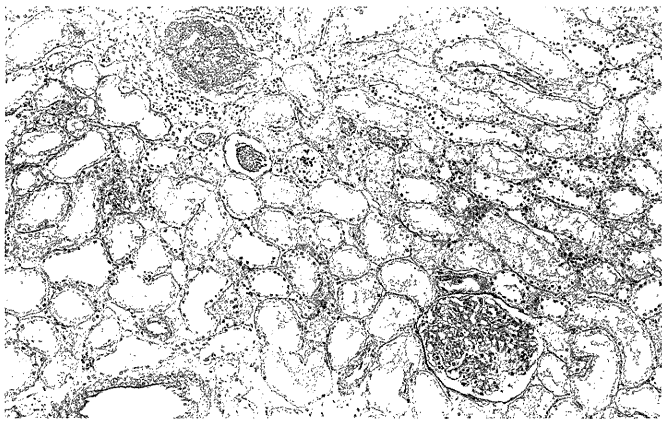

Figure 1. Photomicrograph showing global severe mesangial proliferation, global glomerulosclerosis, tubular atrophy and, interstitial fibrosis (Periodic acid-Schiff; original magnification x 120).

Statistics

All data were statistically analyzed using Statview 5.0 software for Windows (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, proteinuria, and histologic grade of the renal biopsy specimen. A *P* value below 0.05 was considered statistically significant.

Results

The mean age of the 7 male and 9 female patients at presentation was 35 $\pm$ 14 years (range 16 to 62). At presentation, 3 patients (18%) had elevated serum IgA concentrations (110 to 410 mg/dl) and none of the 16 had low serum complement levels. The median follow-up period was 48 months (range 12 to 124). During the follow-up in 16 IgAN, 7 patients (44%) became hypertensive: renal function became impaired in 5 (31%) of these and 2 (13%) progressed a need for hemodialysis 27 and 84 months after initial presentation (events group). Impaired renal function and hypertension developed within a median of 28 (range 3 to 58) and 44 months (range 23 to 77), respectively (Figure 2). Another 9 patients (56%) had persistent abnormalities in urinalysis examinations, although events did not develop (event-free group). The clinical findings were not significantly different between the two groups (Table 1).

We summarized pathological changes in renal biopsy specimens from the 16 patients (Table 2). The Glomerulosclerosis (GS) and Tubulointerstitial damage (TID) scores were significantly different between the groups (P = 0.003 and P = 0.03, respectively), but the hyaline arteriosclerosis (HA) scores and classifications of IgAN were not. Only the renal histological parameters of GS and events were statistically correlated with renal survival (Figure 3).

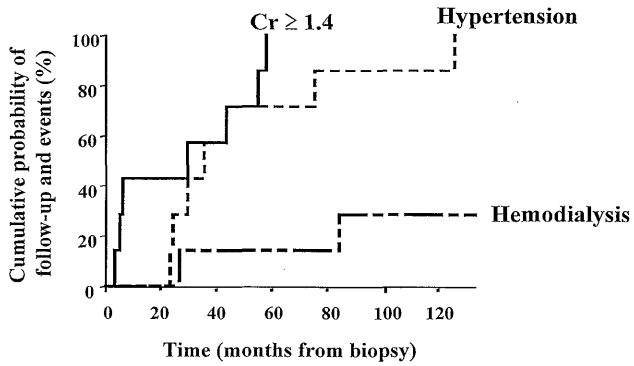

Figure 2. Cumulative probabilities of follow-up and clinical events. The median follow-up was 48 months (range 12 to 124). During follow-up of 16 patients with Immunoglobulin A nephropathy, 7 (44%) became hypertensive: 5 (31%) developed impaired renal function and 2 (13%) progressed hemodialysis 27 and 84 months after initial presentation. Impaired renal function and hypertension developed within a median of 28 (range 3 to 58) and 44 months (range 23 to 77), respectively.

Table 1. Clinical characteristics of groups at the time of presentation that did and did not develop events during subsequent follow-up period

	Events (n = 7)	Event-free (n = 9)	*P* value
Age (years)	39±10	31±16	0.22
Gender (M/F)	2/5	5/4	0.29
Body mass index (kg/mm^2)	21.6±1.7	23.0±3.1	0.11
Serum creatinine (mg/dl)	1.0±0.2	1.0±0.1	0.14
Urine creatinine (mg/dl)	78±26	110±69	0.49
Creatinine clearance (ml/min)	99.7±4.3	98.0±7.8	0.87
Serum Immunoglobulon A (mg/dl)	399±101	313±150	0.12
Fibrinogen	314±83	288±102	0.49
Serum complement titer (U/ml)	38.2±4.9	40.0±7.5	0.95
Uric acid (mg/dl)	6.7±1.1	6.0±1.8	0.31
Macrohematuria	1/6	3/6	0.39
Proteinuria (g/day)	1.5±0.6	1.0±0.6	0.08

Value expressed as mean±SD. n: number of patients

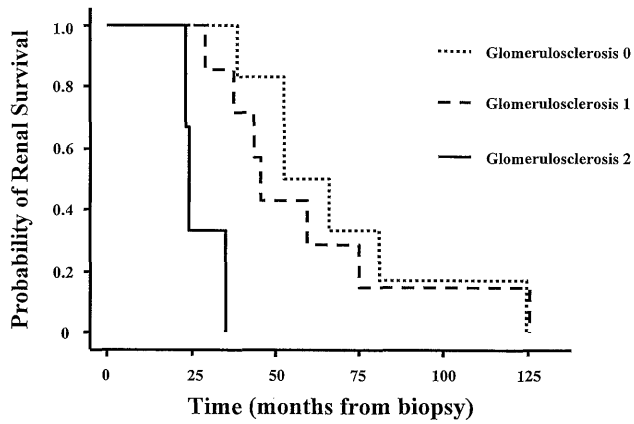

Figure 3. Renal survival rates of patients with immunoglobulin A nephropathy accompanied by proteinuria (≥ 0.5 g per day) assessed by the presence of glomerulosclerosis. Survival rates were significantly higher when severity of glomerulosclerosis was low ($P < 0.01$).

Table 2. Comparison of histopathologic renal findings in patients with immunoglobulin A nephropathy who did and did not develop events

	Events (n = 7)	Event-free (n = 9)	*P* value
Classification of IgAN	3.3±0.7	3.1±1.0	0.86
Glomerulosclerosis	1.4±0.5	0.3±0.5	0.003
Tubulointerstitial damage	2.0±0.9	0.8±1.0	0.03
Hyaline arteriosclerosis	0.6±0.5	0.2±0.4	0.16

Value expressed as mean±SD. n: number of patients

Discussion

We examined the natural history of IgAN among patients who presented with proteinuria. Our findings suggested that the incidence of hypertension and impaired renal function continued to increase with time. Osawa et al.[23] indicated that an optimal level of BP (< 120/80 mmHg) was better than an intermediate level of BP (120/80 ≤ BP < 140/90) in preventing the progression of renal damage in patients with IgAN. Kanno et al.[24] produced evidence indicating that reducing BP confers protective renal effects in patients with mild renal insufficiency accompanied by hypertension in IgAN. Recently, the Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2000 for the Detection, Evaluation, and Treatment of High Blood Pressure recommended a target BP of < 130/85 mmHg for patients with renal disease, and a BP of < 125/75 mmHg in patients with ≥ 1 g/day of proteinuria[25]. Szeto et al.[26] recently reported that IgAN with proteinuria is a progressive disease and recommended life-long follow-up with regular monitoring of blood pressure.

The present study found that the severity of glomerulosclerosis and chronic tubulointerstitial damage significantly correlated with clinical events including subsequent proteinuria, hypertension and impaired renal function. Only the renal histological parameters of glomerulosclerosis and adverse events were statistically correlated with renal survival. The presence of glomerulosclerosis tends to suggest progression, which in turn suggests that although the severity of glomerulosclerosis is the only morphological parameter that independently correlates with renal survival in adult patients with IgAN, information about tubulointerstitial damage and hyaline arteriosclerosis may be useful when the renal pathological characteristics of individual patients are assessed in clinical practice[27,28]. Therefore, we postulate that presence/absence of glomerulosclerosis may be predictable the prognosis of patients with

IgAN accompanied by proteinuria. 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[29,30]. We therefore exclusively focused on chronic irreversible lesions and used a chronicity-based histological grading system that assessed glomerulosclerosis, tubulointerstitial damage and hyaline arteriosclerosis over a long-term follow-up. Although histological grading systems such as classification of IgAN[27], tubular lesions, vascular lesions, IgA deposit typography, and crescents have been used to evaluate the prognosis o IgAN[27,28,30], we believe that this scoring system is convenient, simple to understand as a prognosticator for patients with IgAN. Our methods to determine prognostic factor in IgAN will need evaluating in a larger patients with IgAN.

In conclusion, the severity of glomerulosclerosis may be predictable prognostic factor in patients with IgAN accompanied by proteinuria at the time of the initial biopsy.

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