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【 ORIGINAL ARTICLE 】

Clinical and Pathological Characteristics of Elderly Japanese Patients with IgA Vasculitis with Nephritis: A Case Series

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Abstract:

Objective This case series aimed to identify the clinical and pathological characteristics of elderly patients (≥60 years) with biopsy-proven IgA vasculitis with nephritis (IgAVN).

Methods The clinical and pathological presentation and treatment outcomes were compared between two groups.

Patients Patients with IgAVN who were ≥19 years old at the time of their renal biopsy were divided into elderly (≥60 years) and adult (19-59 years) groups.

Results Of the 23 patients in our study, 13 were elderly. In the elderly group, the median age at the diagnosis was 68 years (range, 60-85 years), with a median follow-up period of 15 months (range, 3-80 months). Twelve elderly patients had comorbidities, including hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, and malignancies. A decrease in the estimated glomerular filtration rate, as well as massive proteinuria and rapidly progressive nephritic syndrome, were more frequent in the elderly group than in the adult group. Furthermore, renal pathological changes, including cellular or fibrocellular crescents, interstitial fibrosis, tubular atrophy, and arteriosclerosis, were more severe among elderly patients than adult patients. All elderly patients were treated with glucocorticoids and had no incidence of end-stage renal disease at the final follow-up; in addition, nine elderly patients had reduced proteinuria with a preserved renal function. Adverse events, including infection, diabetes mellitus, and vascular disorders, were identified in nine patients. Three elderly patients died from severe infections.

Conclusion IgAVN in elderly patients is characterized by severe renal involvement. Elderly patients are at higher risk than adults for treatment-related adverse events.

Key words: adults, elderly, purpura, Henoch-Schönlein, glomerulonephritis

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Introduction

Immunoglobulin A vasculitis (IgAV), also known as Henoch-Schönlein purpura, is a leukocytoclastic vasculitis characterized by the deposition of IgA immune complexes in small vessels. Renal involvement is common in IgAVN, along with involvement of the skin, joints, and gastrointestinal system. IgAV primarily affects children and is less frequent in adults. The annual incidence of IgAV in children is estimated to be 14 cases per 100,000 (1), but it is only 1.3 per 100,000 in adults with a mean age of 50 years at initial presentation (2).

Although IgAV with nephritis (IgAVN) has been exten-

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sively studied in children, its natural history in adults, especially elderly patients, is not fully understood because of its rarity. However, we do know that renal involvement occurs more frequently in adults (up to 45-85%) than in children (30-40%) (3, 4). Furthermore, the risk of progression to renal insufficiency, which ranges from 5% (5, 6) to 15% (7-9) in children, seems to be much higher in adults, at approximately 30% (0-50%) (4, 10-12). The onset of IgAVN in patients over 50 years of age seems to be a strong predictor of severe renal failure (4, 13). However, only a few reports have focused on the clinical and histological features of IgAVN in elderly patients (≥60 years of age), including their response to treatment.

Therefore, our aim in this case series was to investigate the renal manifestations and pathological findings of biopsy-proven IgAVN in 13 elderly Japanese patients compared to those of adult patients (19-59 years of age) to clarify the clinical and histological characteristics of IgAVN among elderly individuals.

Materials and Methods

Patients

Of all of the patients who underwent renal biopsies between January 2002 and December 2012 at Jikei University Hospital and Tokyo Saiseikai Central Hospital, those older than 18 years of age at the time of the biopsy and diagnosed with IgAVN were enrolled in this study. The institutional ethics committees of both institutions approved this study. All procedures were performed in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare of Japan.

The diagnosis of IgAVN was made based on a modification of the European League Against Rheumatism/the Paediatric Rheumatology International Trials Organisation/the Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) classification criteria: purpura or petechiae with lower limb predominance and unrelated thrombocytopenia and the presence of urinary abnormalities, renal failure, and predominant mesangial IgA deposits on a renal biopsy. All patients except three underwent a skin biopsy and were confirmed to have leukocytoclastic vasculitis with predominant IgA deposits. The three patients without a skin biopsy did not have pre-existing malignant disease. We excluded patients with primary and secondary IgA nephropathy. In addition, patients with other diseases associated with nephropathy and a purpuric rash, such as systemic lupus erythematosus or cryoglobulinemia, were excluded. The remaining 23 patients were included in our study. Based on their age at the time of the biopsy, the patients were classified into the elderly group (≥60 years of age) or the adult group (19-59 years of age).

Definitions and Measurements

The following clinical and pathological features were compared between the two groups: sex, mean arterial pressure, hypertension at the diagnosis, joint and gastrointestinal (GI) involvement, the estimated glomerular filtration rate (eGFR), urinary protein excretion, a clinical diagnosis of renal involvement, global sclerosis, cellular or fibrocellular crescents, interstitial fibrosis and tubular atrophy (IF/TA), arteriosclerosis, prevalence of steroid treatment, and treatment outcomes. The eGFR was calculated using the modified three-variable equation previously reported for estimating the GFR in the Japanese population (14): $eGFR=194\times age^{-0.287}\times sCr^{-1.094}\times 0.739$ (if female), where sCr is the serum creatinine level. A clinical diagnosis of renal involvement was based on the modified classification of the World Health Organization (WHO) and included chronic nephritic syndrome, acute nephritic syndrome, recurrent or persistent hematuria, and rapidly progressive nephritic syndrome (15, 16).

The following renal pathologies were evaluated: glomeruli with global sclerosis, cellular/fibrocellular crescents, and endocapillary hypercellularity were reported as the percentage of affected glomeruli over all glomeruli in the biopsy specimen. The IF/TA was expressed as the area occupied by the fibrosed interstitium and the atrophied tubules over the entire tubulointerstitial area in the biopsy specimen (17). Arteriosclerosis was graded from 0-2, as described in a previous report (18), with 0 indicating no intimal thickening, 1 indicating a thickening of the intima that was less than the thickness of the media, and 2 indicating a thickening of the intima that was the same as or greater than the thickness of the media.

The treatment protocols were determined by the attending physicians in accordance with the disease activity and severity. The following treatments and outcomes were evaluated: the prevalence of glucocorticoid or other immunosuppressant therapy, the prevalence of end-stage kidney disease, the prevalence of a decrease in eGFR ≥30% of the baseline value at the time of the diagnosis, the prevalence of a urinary protein excretion level <0.3 or <1.0 g/gCr at the last visit, the prevalence of adverse events during the course of treatment, and treatment-related adverse events and death.

Statistical analyses

The Wilcoxon-Mann-Whitney two-sample rank-sum test was used to compare continuous variables between the two groups, while Fisher's exact test was used to compare ordinal variables. Continuous variables were expressed as the median and the range or interquartile range. All statistical analyses were performed using EZR, which is a graphical user interface for R (19). A p value <0.05 was considered to be statistically significant.

Table 1. Clinical Characteristics of Elderly Patients with IgAVN at the Time of Renal Biopsy.

	Age (years)	Sex	Comorbidity					Extra-renal involvement		eGFR (mL/min/1.73 m^2)	UPE (g/gCr)	Clinical diagnosis
			HTN	DM	CKD	CVD	MD	Joints	GI			
Case 1	85	F	+	+	+	+†	-	-	+	40	4.3	NS
Case 2	80	F	+	-	-	-	-	-	+	66	0.8	CNS
Case 3	76	F	-	-	-	-	-	-	-	72	1.3	CNS
Case 4	75	F	+	-	-	+‡	-	-	+	17	6.0	RPNS
Case 5	71	M	+	-	-	+§	-	-	-	47	1.8	CNS
Case 6	69	M	-	+	+	-	-	-	-	38	1.2	CNS
Case 7	68	F	-	-	-	-	-	-	-	63	7.0	ANS
Case 8	63	M	+	-	-	+†	+††	-	-	41	7.2	RPNS, NS
Case 9	63	M	+	-	-	-	-	-	-	87	4.4	CNS
Case 10	62	M	+	+	+	+†, §	-	-	-	29	6.3	RPNS, NS
Case 11	61	M	-	-	-	+§, ¶	+‡‡	+	+	49	9.8	RPNS, NS
Case 12	61	M	+	+	+	-	-	-	-	28	10.5	RPNS, NS
Case 13	60	M	+	-	-	-	+§§	-	-	56	7.4	ANS, NS
The median values or the totals¶¶	68	M/F 8/5	9	4	4	6	3	1	4	36	6.0	NS/CNS/RPNS/ ANS 6/5/5/2

†Coronary artery diseases, ‡Arterio-venous block, §Chronic atrial fibrillation, ¶Rheumatic mitral steno-insufficiency, ††Nasal squamous cell carcinoma, ‡‡Colon cancer, §§Acute myeloid leukemia, ¶¶Sex, comorbidity and clinical diagnosis are expressed as the totals.

F: female, M: male, HTN: hypertension, DM: type 2 diabetes mellitus, CKD: chronic kidney disease, CVD: cardiovascular disease, MD: malignant disease, GI: gastrointestinal tract, eGFR: estimated glomerular filtration rate, UPE: urinary protein excretion, NS: nephrotic syndrome, CNS: chronic nephritic syndrome, RPNS: rapidly progressive nephritic syndrome, ANS: acute nephritic syndrome, IgAVN: IgA vasculitis with nephritis

Results

Clinical and pathological characteristics of the elderly group

The elderly group included 8 men and 5 women with a median age of 68 years (range, 60-85 years) (Table 1). Of these, 12 patients had ≥1 comorbidity prior to the time of the renal biopsy: 9 had hypertension; 4 had diabetes mellitus; 4 had chronic kidney disease (CKD); 6 had cardiovascular diseases (coronary artery diseases and chronic atrial fibrillation); and 3 had malignant diseases (nasal squamous cell carcinoma, colon cancer, and acute myeloid leukemia). Two patients (cases 8 and 13) developed IgAVN during the course of treatment for a malignancy. Most patients in the elderly group presented with purpura as the first clinical manifestation of IgAVN, except for one patient (case 11) who presented with joint involvement. Four patients had GI involvement. The median eGFR was 36 mL/min/1.73 m^2 (range, 17-87), with a median urinary protein excretion of 6.0 g/gCr (range, 0.8-10.5). Five of the 13 patients presented with a rapidly progressive nephritic syndrome. Regarding renal pathologies, all elderly patients had cellular or fibrocellular crescents and endocapillary hypercellularity to varying degrees, in addition to chronic lesions, such as global sclerosis, IT/FA, and arteriosclerosis (Table 2).

A between-group comparison of clinical and pathological manifestations

To clarify the clinical and pathological features of elderly patients at the time of the renal biopsy, we compared the clinical and laboratory variables between the two groups (Table 3). The median age of the adult group was 31 years (range, 19-59). The mean arterial pressure was comparable between the 2 groups (p=0.40), whereas the prevalence of hypertension was significantly higher among elderly patients than among adult patients (69% vs. 0%, p=0.0016). Joint and GI involvement was comparable between the two groups (p=0.28 and 1.0, respectively). The eGFR at the time of the renal biopsy was lower in the elderly group than in the adult group (36 vs. 51 mL/min/1.73 m^2, p=0.042). The prevalence of high proteinuria (>3.0 g/gCr) and rapidly progressive nephritic syndrome was greater among elderly patients than among adult patients (69% vs. 20%, p=0.036; and 38% vs. 0%, p=0.045, respectively). Furthermore, pathological findings were more frequently observed among elderly patients than among adult patients, including cellular or fibrocellular crescents (20% vs. 5%, p=0.008), IT/FA (20% versus 5%, p=0.012), and arteriosclerosis (score 2 vs. 0, p<0.001).

Treatments and outcomes for the elderly group

The median follow-up period was 15 months (range, 3-80) (Table 4). All elderly patients were treated with corticosteroids, and no other immunosuppressive agents were used. At the end of the follow-up period, none of the pa-

Table 2. The Severity of Renal Pathology Findings among Elderly Patients with IgAVN.

	Global sclerosis (%)†	Cellular or fibrocellular crescents (%)†	Endocapillary hypercellularity (%)†	IF/TA (%)‡	Arteriosclerosis (score 0-2)
Case 1	0	100	100	20	2
Case 2	10	10	10	5	2
Case 3	10	20	10	20	2
Case 4	10	70	50	20	1
Case 5	10	10	30	5	0
Case 6	20	10	10	20	1
Case 7	10	10	20	10	1
Case 8	10	40	60	10	2
Case 9	10	30	30	5	2
Case 10	20	30	30	50	0
Case 11	0	20	20	10	1
Case 12	80	20	20	50	2
Case 13	0	20	20	30	2
Median values	10	20	20	20	2

†Percentage of glomeruli affected, ‡Percentage of the tubulointerstitial area occupied with interstitial fibrosis or tubular atrophy.

IF/TA: interstitial fibrosis and tubular atrophy, IgAVN: IgA vasculitis with nephritis

tients were on dialysis, although two patients temporarily required dialysis during the course of their treatment (cases 10 and 12). These two patients had overt diabetic nephropathy before the onset of nephritis. A deterioration in the renal function (eGFR reduction rate ≥30% from baseline) was identified in 4 patients (case 1, 3, 10, and 12). Of these patients, three had pre-existing diabetes mellitus and CKD. Furthermore, these patients showed more severe IT/FA with a higher prevalence of persistent proteinuria (>1.0 g/gCr) at the final follow-up visit than the other 9 elderly patients with a preserved renal function. These 9 patients had a urinary protein excretion level <1.0 g/gCr, while the other 7 had a urinary protein excretion level <0.3 g/gCr. The rate of patients who achieved a protein excretion level of <0.3 g/gCr was not significantly different between the elderly and the adult groups (Table 3).

Nine elderly patients experienced adverse events during the follow-up period: three developed an infection, two developed steroid-induced diabetes mellitus, one developed malignant mesothelioma, one developed duodenal perforation, and two developed vascular disorders (peripheral artery disease, cerebral infarction, or deep venous thrombosis). In addition, three elderly patients died from severe infections, including pneumonia, sepsis, urinary tract infection, and infectious endocarditis. Infections and the development of diabetes mellitus were considered to be treatment-related adverse events. These adverse events were observed more often in the elderly group than in the adult group (Table 3).

Discussion

The prevalence of IgAVN varies with age. The patients involved in our study showed a bimodal distribution of the age at the diagnosis of IgAVN, with peaks at 20-29 and 60-69 years. Thus, in our study, we classified patients with IgAVN into two groups, based on the age at the diagnosis: elderly patients ≥60 years of age and adult patients 19-59 years of age. The age distribution was similar to that of patients registered for the Japan Renal Biopsy Registry (J-RBR), with peaks at 30-39 and 60-69 years (20). A decline in the eGFR, massive proteinuria, and rapidly progressive nephritic syndrome were observed more often in the elderly group than in the adult group. Although the differences in proteinuria were not statistically significant, this may simply be because of the small sample size. These clinical manifestations among elderly patients in our study group were similar to those reported in the J-RBR database (Table 5). Most elderly patients in our study had various types of pre-existing comorbidities at the time of the diagnosis, including hypertension, type 2 diabetes mellitus, cardiovascular disease, and malignant diseases (nasal squamous cell carcinoma, colon cancer, and acute myeloid leukemia) while the J-RBR database reported on hypertension alone. A higher incidence of hypertension among elderly patients than among adult patients has previously been reported (4, 13, 20). Although the relationship between IgAVN and malignant diseases is unclear, several reports have suggested an association between malignancy and IgAV (21-23). Mitsui et al. identified an underlying malignancy in 23 of 53 (43.4%) patients over 40 years of age who had a diagnosis of IgAV (21). In their report, lung cancer and hematological diseases were the most common malignancies. Another study reported lung (14%) and upper respiratory and digestive tract (8%) malignancies to be the leading cause of mortality among adults with IgAVN (4).

The renal biopsy findings in our case series revealed cellular and fibrocellular crescents, IF/TA, and arteriosclerosis to be more severe in elderly patients than in adult patients.

Table 3. Comparison of Clinical and Pathological Manifestations between Elderly and Adult Patients with IgAVN.

	Elderly patients ≥60 years (n=13)	Adult patients 19-59 years (n=10)	p values†
Age, years	68 [62, 75]	31 [23, 42]	
Male sex, % (n)	62 (8)	80 (8)	0.40
MAP, mmHg	95 [93, 110]	91 [86, 101]	0.27
HTN, % (n)	69 (9)	0 (0)	0.0016*
Joint involvement, % (n)	7 (1)	30 (3)	0.28
GI involvement, % (n)	30 (4)	30 (3)	1.0
eGFR, mL/min/1.73 m^2	36 [28, 63]	51 [47, 64]	0.042*
UPE, g/gCr	6.0 [1.8, 7.2]	2.0 [1.0, 2.7]	0.062
UPE ≥3.0 g/gCr	69 (9)	20 (2)	0.036*
RPNS, % (n)	38 (5)	0 (0)	0.045*
Nephrotic syndrome, % (n)	46 (6)	10 (1)	0.088
Pathological findings			
Global sclerosis, %	10 [10, 10]	5 [0, 10]	0.37
Cellular or fibrocellular crescents, %	20 [10, 30]	5 [0, 10]	0.008*
Interstitial fibrosis and tubular atrophy, %	20 [10, 20]	5 [5, 10]	0.012*
Arteriosclerosis (score 0 to 2)	2 [1, 2]	0	<0.001*
Treatment and outcomes			
Duration of follow-up, mo	16 [9, 45]	28 [24, 57]	0.21
Steroid treatment, % (n)	100 (13)	70 (7)	0.067
ESKD	0 (0)	0 (0)	-
≥30% decrease in eGFR, % (n)	30 (4)	10 (1)	0.33
UPE <1.0 g/gCr at the last visits, % (n)	61 (8)	100 (10)	0.045*
UPE <0.3 g/gCr at the last visits, % (n)	46 (6)	60 (6)	0.68
Adverse events during treatment curses, % (n)	69 (9)	10 (1)	0.009*
Treatment-related adverse events‡, % (n)	46 (6)	0 (0)	0.019*
Death, % (n)	23 (3)	0 (0)	0.22

n represents the number of patients. Other values are expressed as the median values with interquartile range [IQR].

†p<0.05 was defined as statistically significant. Wilcoxon-Mann-Whitney two-sample rank-sum test or Fisher's exact test was used. ‡Treatment-related adverse events refer to infectious disease and steroid-induced diabetes mellitus. *statistically significant.

MAP: mean arterial pressure, HTN: hypertension, GI gastrointestinal, UPE: urinary protein excretion, RPNS: rapidly progressive nephritic syndrome, ESKD: end-stage kidney disease, IgAVN: IgA vasculitis with nephritis, eGFR: estimated glomerular filtration rate

A French group further reported a higher incidence of glomerular fibrinoid necrosis among patients over 60 years of age compared to that in patients under 30 years of age. According to the J-RBR database, endocapillary proliferative glomerulonephritis and crescentic/necrotizing glomerulonephritis were more common pathological diagnoses in elderly patients than in adult patients; however, those authors did not investigate the severity of the histological findings as we did in our study. Similar to the findings of the J-RBR, all elderly patients in our study had endocapillary hypercellularity of varying degrees, although the involvement was not significantly different between the elderly group and the adult group. Of note, elderly patients presented with more severe renal pathological changes than adult patients, including not only chronic lesions, such as IF/TA and arteriosclerosis, but also acute lesions, such as fibrinoid necrosis, cellular or fibrocellular crescents, and endocapillary hypercellularity. Although the underlying mechanisms remain unclear, one possible explanation might be an age-related decrease in the clearance of immune complexes from the glomeruli (24, 25).

Most patients in our study group received glucocorticoid therapy and achieved improvements in the renal function, including a reduction in urinary protein excretion and maintenance of a sufficient eGFR. However, in patients with preexisting diabetes mellitus and CKD, more severe IT/FA lesions and persistent proteinuria resulted in a decline in the renal function.

There are no widely accepted treatment regimens for adult patients with IgAVN, especially elderly patients. Recently, a French multicenter cohort study reported that corticosteroid therapy as a single therapeutic agent was a reasonable first-

Table 4. Treatments and Outcomes for Elderly Patients with IgAVN.

	Treatments	Initial dose of PSL (mg/kg)	Duration of follow-up (mo)	% decrease in eGFR at the last visits (%)‡	UPE at the last visits (g/gCr)	Adverse events during treatment courses
Case 1	OS	0.7	8	40	1.8	CMVI, pneumonia, sepsis, death
Case 2	OS	0.7	6	0	<0.3	none
Case 3	SP†+OS	0.6	20	30	3.8	DM, HTN, DL
Case 4	SP†+OS	0.7	64	0	<0.3	DM
Case 5	OS	0.3	55	10	<0.3	PAD
Case 6	SP†+OS	0.5	8	0	<0.3	none
Case 7	OS	0.6	80	20	<0.3	none
Case 8	OS	0.5	20	0	0.9	CI, DVT
Case 9	OS	0.6	45	10	<0.3	DM, malignant mesothelioma
Case 10	OS	0.4	10	60	10.7	pneumonia, death
Case 11	SP†+OS	0.7	9	20	0.4	UTI, IE, sepsis, death
Case 12	OS	0.4	3	30	4.6	duodenal perforation
Case 13	OS	0.6	15	10	<0.3	none
Median values or totals§	SP+OS/OS 4/9	0.6	15	10	0.3	infectious diseases¶/DM/vascular disorders††/death 3/2/2/3

†Intravenous administrations of 0.5 g of methylprednisolone for 3 consecutive days. ‡The percentage decrease in eGFR from that at renal biopsy. §Treatments and adverse events during treatment courses are expressed as the total. ¶Infectious diseases refer to CMVI, pneumonia, sepsis, and UTI. ††Vascular disorders refer to PAD, CI, and DVT.

OS: oral steroid therapy with prednisolone, SP: steroid pulse therapy, PSL: prednisolone, eGFR: estimated glomerular filtration rate, UPE: urinary protein excretion, CMVI: cytomegalovirus infection, DM: steroid-induced diabetes mellitus, HTN: hypertension, DL: dyslipidemia, PAD: peripheral artery disease, CI: cerebral infarction, DVT: deep venous thrombosis, UTI: urinary tract infection, IE: Infections endocarditis, IgAVN: IgA vasculitis with nephritis

Table 5. Comparison of Clinical Manifestations at the Time of Diagnosis between the Elderly and Adult Patients with IgAVN in Our Study and Those in the J-RBR Database.

	Our cases		J-RBR database[20]	
	Elderly† (n=13)	Adult‡ (n=10)	Elderly§ (n=96)	Adult¶ (n=259)
Age (years), median [IQR]	68 [62, 75]	31 [23, 42]	72 [68, 76]	43 [30, 59]
Sex, male/female	8/5††	8/2††	49/47††	119/140††
Hypertension, % (n)	69.2 (9)	0 (0)	67.7 (65)	41.3 (107)
Rapidly progressive nephritic syndrome, % (n)	38 (5)	0 (0)	13.5 (13)	3.4 (9)
Nephrotic syndrome, % (n)	46 (6)††	10 (1)††	18.8 (18)	10.8 (28)
Estimated GFR, mL/min/1.73 m^2‡‡	41.2±19.1	60.4±22.4	45.4±24.3	74.2±28.6
Proteinuria (g/gCr)‡‡	5.23±3.24††	2.46±2.51††	4.08±3.64	2.53±2.84

†≥60 years of age. ‡Between 19 and 59 years of age. §≥65 years of age. ¶Between the ages of 19 and 64 years. ††Not statistically significant. ‡‡Mean±standard deviation (SD).

IgAVN: IgA vasculitis with nephritis, IQR: interquartile range, J-RBR: Japan renal biopsy registry

line therapy for adult patients with IgAV (26). However, the study was not designed for elderly patients, and it did not assess the efficacy and safety of treatments in this age group. In our study, 9 of 13 elderly patients experienced adverse events during the course of their treatment, including infections, steroid-induced diabetes mellitus, hypertension, dyslipidemia, vascular disorders (e.g., peripheral artery disease, cerebral infarction, deep venous thrombosis), malignant mesothelioma, and duodenal perforation. Three patients died from severe infections, which we deemed to be partly associated with treatment. Similar findings were reported in studies evaluating adults with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (27-29). AAV often occurs in older patients (>65 years of age), with the prognosis being worse in older patients than in younger ones due to a greater involvement of the kidneys and greater prevalence of adverse events secondary to treatment (29). According to a Japanese nationwide early survey of AAV/rapidly progressive glomerulonephritis (RPGN), Japanese patients developed AAV at an older age than did patients from other countries, with a lower survival rate partly because of opportunistic infections (28). In addition, treatment using a high dose of oral prednisolone (≥0.8 mg/kg/day) has been associated with a lower survival rate among patients

with AAV/RPGN, whereas the initial prednisolone dosage did not affect the renal survival. Therefore, the treatment guidelines for Japanese patients with AAV/RPGN recommend the use of a reduced initial dose of prednisolone, with or without immunosuppressants, for elderly patients (>70 years old).

None of our patients received an initial high dose of oral prednisolone or immunosuppressants. In the prospective cohort of the "Japanese patients with myeloperoxidase (MPO)-ANCA-associated vasculitis" (JMAAV) study, the total amount of glucocorticoid used was associated with several glucocorticoid-associated adverse events, including infections, diabetes mellitus, and bone fractures (27). A review of our three cases that died suggested that their underlying disease conditions likely influenced their poor prognoses in addition to the initial and total dose of glucocorticoid used and their age at the diagnosis. Cases 1 and 10 had a longstanding history of poorly controlled type 2 diabetes mellitus and pre-existing CKD. The cumulative doses of glucocorticoid administered in these patients were comparable to those for other elderly patients without severe infections (data not shown). While case 11 received a higher dose of glucocorticoid therapy than other elderly patients, he had an untreated rheumatic mitral steno-insufficiency and ultimately died of uncontrollable infectious endocarditis originating from a urinary tract infection. Taken together, these findings suggest that further titration of glucocorticoid regimens should be considered for elderly patients, especially those with these underlying disease conditions.

There are some limitations to our study that need to be noted. First, as the number of patients was limited, there is a possibility of selection bias, especially with regard to comorbidities and adverse events during treatment, with the prevalence of extra-renal complications increasing with age. Thus, it is not possible to exclude the effects of age-related complications from our findings. Second, we used a cut-off of 60 years to define 'elderly,' based on the definition of the United Nations Population Fund, although the cut-off age used by the WHO is 65 years. As described above, IgAVN in our patients had a second peak of prevalence in the age group of 60-69 years; most of our patients were 60 to 64 years old and exhibited clinical and pathological features similar to those previously reported for patients ≥65 years of age.

In summary, we showed that the clinical and pathological presentation of patients with IgAVN was more severe in elderly patients than in adult patients. All elderly patients received glucocorticoid therapy due to their severe presentation. While glucocorticoid therapy resulted in beneficial renal outcomes in most elderly patients, it also caused severe adverse events in some patients, especially those with underlying disease conditions, such as pre-existing poorly controlled type 2 diabetes mellitus and CKD or mitral valve disease in the elderly group. Therefore, the optimum treatment regimen for elderly patients should be explored in future studies.

The authors state that they have no Conflict of Interest (COI).

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