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The outcome and a new ISN/RPS 2003 classification of lupus nephritis in Japanese

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The outcome and a new ISN/RPS 2003 classification of lupus nephritis in Japanese.

Background. A considerable diversity in prognosis is seen with lupus glomerulonephritis (LGN). Hence, the clinical usefulness of a recent International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification to judge the long-term outcome of human LGN has been investigated.

Methods. We studied retrospectively 60 subjects with LGN (7 males, 53 females, mean age of 33 years old) who underwent renal biopsies and were followed from 1 to 366 months, with a mean of 187 months. We diagnosed renal pathology as classes, active and sclerosing lesions, according to the new and WHO1995 classification of LGN, and analyzed the clinicopathologic factors affecting to the prognosis of LGN.

Results. New classification got much higher consensus in the judgment of classes (98% vs. 83%, $P = 0.0084$). The group of Class IV-S ($N = 6$) or IV-G ($N = 17$) at initial biopsies showed higher rate of end-stage renal failure (ESRF) compared with that of Class I, II, III or V (40.9% vs. 2.6%, $P < 0.001$). The mean 50% renal survival time of Class IV was 189 ± 29 months, and patients with Class IV-S tended to have a poorer prognosis (95 ± 22 months for IV-S vs. 214 ± 35 months for IV-G, $P = 0.1495$). Class IV was also selected as the most significant risk factor for ESRF by stepwise model ($P = 0.002$). In subanalysis for ESRF in Class IV (-S or –G), treatment including methylprednisolone pulse therapy was only selected as a significant improving factor for primary outcome ($P = 0.034$). In addition, activity index was the significant risk factor of death and/or ESRF after initial renal biopsies ($P = 0.043$). As for actuarial patient death during all follow-up periods, complications with anti-phospholipid syndrome or nephrotic syndrome were significant risk factors ($P = 0.013$, $P = 0.041$, respectively).

Conclusion. New ISN/RPS 2003 classification provided beneficial pathologic information relevant to the long-term renal outcome and the optimal therapy preventing ESRF and/or death in patients with LGN.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with the characteristic development of autoantibodies to DNA and other nuclear antigens, as well as to membrane molecules such as phospholipids. About 20% to 50% of unselected patients with lupus are reported to have abnormal urine tests in their early disease courses, and up to 60% of adults may go on to develop overt renal abnormalities. A considerable diversity in prognosis is seen with lupus nephritis, however. The glomerular lesions in lupus nephritis are so variable, leading to a more complex clinical expression of this disease [1–2].

Concerning the classification of lupus nephritis, the first 1974 World Health Organization (WHO) classification was examined in 1978 by Appel et al [3]. In 1982, the 1974 WHO classification was modified. This 1982 WHO classification [4] introduced subdivisions for Class III and IV based on the presence of active, chronic, or mixed types of glomerular injury. Austin et al [5] devised a system of applying semiquantitative scores for activity and chronicity by grading and adding the individual morphologic components in a given biopsy as a guide to treatment and prognosis. Activity and chronicity scores have been used as an adjunct to the WHO classification of lupus nephritis [5, 6]. In 1995, segmental glomerular capillary wall necrosis, a lesion also characteristic of glomerular injury in systemic vasculitis, was paid much attention [7]. In this notion, Najafi et al [8] revealed the poor outcome of lupus glomerulonephritis (LGN) with segmental necrosis involving over 50% of glomeruli as compared to

[1]The centers and investigators participating in this study are listed in the **Appendix**.

Key words: lupus nephritis, nephrotic syndrome, immunosuppressant, outcome, anti-phospholipid syndrome.

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category IV lupus nephritis (diffuse proliferative glomerulonephritis).

In order to accommodate the clinicopathologic and pathogenetic insights, a new revised classification was proposed recently [9]. This revised classification introduced several important modifications concerning quantitative and/or qualitative differences between Class III, IV, and V lesions. Like the preceding classifications, the new classification is based exclusively on glomerular pathology and, as such, represents a classification of LGN.

Hence, we investigated the clinical usefulness of a recent International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LGN to judge the long-term outcome of human LGN in a retrospective study. We found that new ISN/RPS 2003 classification provides beneficial pathologic information relevant to the renal outcome of LGN.

METHODS

Patients and treatments

We retrospectively enrolled 60 Japanese subjects (7 males and 53 females, aged 14 to 63 years, mean 33 years) with SLE diagnosed by the adequate evaluations of the 1982 or 1997 American Rheumatism Association [10–11], who were admitted to the First Department of Internal Medicine of Kanazawa University Hospital, or its affiliated hospitals, between 1973 and 2000. Clinical state on admission was judged as acute nephritic syndrome, rapidly progressive nephritic syndrome, recurrent or persistent hematuria, chronic nephritic syndrome, and nephrotic syndrome, as shown in clinical syndromes and glomerular histopathology of WHO classification [4, 7]. We followed these patients for at least 3 years, or until end-stage renal failure (ESRF) or death since the first renal biopsies (from 1 to 366 months, mean 187 months). Diagnosis of LGN was confirmed in all patients by percutaneous needle renal biopsy. We also did renal biopsies in 6 patients at clinical relapse of nephritis, and in 22 patients as follow-up biopsies to judge the disease activities. The patients were treated nonrandomly depending on the judgment of the doctors in charge of each case, with either no immunosuppressant or supportive therapy ($N = 2$), oral corticosteroid (steroid) (prednisolone 20-60 mg/day, $N = 58$), including intravenous methylprednisolone pulse therapy (500-1000 mg/day $\times$ 3 days, 1–3 times, $N = 35$), steroid with oral immunosuppressants such as cyclophosphamide, azathioprine, mizoribine, or cyclosporine ($N = 17$), or high-dose intravenous cyclophosphamide (10 mg/kg/2–4 weeks, 2–4 times), followed by oral immunosuppressants ($N = 4$). Informed consent was obtained for all renal biopsies and treatments. Anti-phospholipid antibody syndrome (APS) was diagnosed according to the 1989 criteria of Harris and Hughes [12], or the 1999 Sapporo criteria [13].

Histopathologic studies

Light microscopic examination. For light microscopic examination (LM), renal biopsy specimens were fixed in 10% phosphate-buffered formalin (pH 7.4), embedded in paraffin, and sliced into 4-μm sections. These specimens were stained with hematoxylin and eosin, periodic acid Schiff reagent, Mallory-azan, and periodic acid silver methenamine, and were examined by light microscopy, with the criteria of the new WHO classification. In brief, Class I, minimal mesangial LGN; Class II, mesangial proliferative LGN, showing purely mesangial hypercellularity of any degree and/or mesangial matrix expansion; Class III, focal LGN involving <50% of the total number of glomeruli; Class IV, diffuse segmental or global LGN involving 50% or more of the total number of glomeruli either segmentally or globally. According to the new classification, Class IV is divided into diffuse segmental (IV-S), when >50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G), when >50% of the involved glomeruli have global lesions. Class V is membranous LGN. Class VI is advanced sclerotic LGN with more than 90% of glomeruli globally sclerosed without residual activity. The frequency of active and chronic lesions was determined, and the "activity index (AI)" and "chronicity index (CI)" of the histologic appearance were also calculated according to the National Institutes of Health scores by Austin et al [5]. We also classified all biopsied specimens according to the 1995 WHO classification [7].

Renal tissue specimens were examined by two pathologists with no knowledge of the patients' clinical condition to establish the diagnosis by standard pathologic methods alone.

Immunofluorescent examination. Fresh specimens obtained from needle biopsies were embedded in OCT compound, snap frozen in n-hexane cooled with a mixture of dry ice and acetone, and cut into 6-μm sections on a cryostat (Tissue-Tek II systems; Miles, Naperville, IL, USA). Sections were treated with fluorescein isothiocyanate (FITC)-labeled antihuman immunoglobulin (Ig) G (γ-chain), IgA (α-chain), and IgM (μ-chain) sheep IgG/F (ab') 2 antibodies, and FITC-labeled antihuman C3 and C1q sheep IgG antibodies (Cappel, West Chester, PA, USA) for immunofluorescent studies.

Electron microscopic examination. A part of biopsied specimens was fixed with glutaraldehyde and osmium tetroxide, embedded in Epon 812 (Oken Shoji Co., Tokyo, Japan), sliced into 0.1-μm sections, double-stained with uranyl acetate and lead citrate, and examined under the electron microscope (Hitachi H-600, Hitachi Co., Tokyo, Japan). For this study, specimens were examined with emphasis on subendothelial, subepithelial, and intramembranous electron dense deposits.

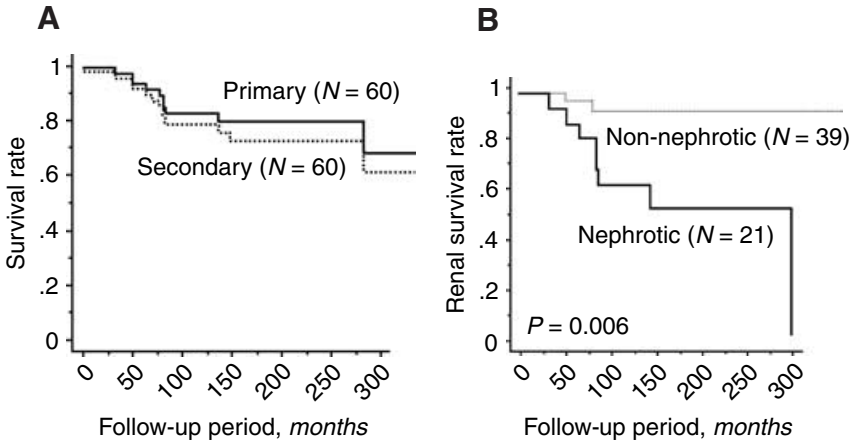

Fig. 1. The primary and secondary outcomes of the retrospective analysis of 60 Japanese subjects with lupus glomerulonephritis since 1973. Primary and secondary outcomes of all subjects were 82% and 78% at 10 years, and 80% and 73% at 20 years, respectively (*A*). Primary outcome of subjects with nephrotic syndrome ($N = 21$) was significantly poor as compared to that of subjects without nephrotic syndrome ($N = 39$) (*B*). The mean time of 50% renal survival in subjects with nephrotic syndrome was 200 ± 29 months ($P = 0.0007$ by the Kaplan and Meier life-table method).

Clinical evaluation

Baseline clinical data were extracted from hospital records. They included values of serum creatinine, serum albumin, 24-hour urine protein excretion, serum levels of complements (C3, C4, CH50), and anti-phospholipid antibodies or lupus anticoagulants.

Clinical status was assessed according to Japanese clinical categories employing the criteria of nephrotic state, presence of marked proteinuria greater than 3.5 g/day or 3+ (300 mg/dL) to 4+ (1000 mg/dL) by Multistics (Miles), and hypoalbuminemia (less than 30 g/L). Renal dysfunction was defined as a serum creatinine level of greater than 132.6 μmol/L (1.5 mg/dL), or an endogenous creatinine clearance of less than 60 mL/min. ESRF was defined as the need for hemodialysis, peritoneal dialysis, or renal transplantation. Primary outcome was defined as ESRF, and secondary outcome as patients' death and/or ESRF.

Statistical analysis

Statistical analyses were performed using Kruskal-Wallis nonparametric analysis of variance test and Wilcoxon rank-sum test for continuous data, and Fisher exact test for categorical data, the Mantel-Cox log-rank test, and the Kaplan and Meier life-table method for renal or patients' survival. The independent risk factors for primary and secondary outcomes were performed with the Cox proportional hazards model. Values were expressed as mean ± standard error of mean (SEM). *P* values of less than 0.05 were considered statistically significant. SAS software (Cary, NC, USA) was used for the statistical calculation [14].

RESULTS

Clinical findings and outcomes of lupus glomerulonephritis

Twenty-one patients (35%) were diagnosed as nephrotic syndrome on admission, two (3.3%) as acute nephritic syndrome, and two (3.3%) as rapidly progressive nephritic syndrome according to the WHO criteria. Thirty-five other patients showed urinary abnormality, such as microscopic hematuria and/or proteinuria. Primary and secondary outcomes of all patients were 82% and 78% at 10 years, and 80% and 73% at 20 years, respectively (Fig. 1A). One patient with rapidly progressive nephritic syndrome died of pulmonary infection at onset. Another patient of rapidly progressive nephritic syndrome reached ESRF after 86 months, but survived with hemodialysis for 21 years from the initial diagnosis at 1983. Two patients with acute nephritic syndrome had Class IV-G (A) LGN with diffuse endocapillary proliferation at onset, and entered remission by immunosuppressive therapies. Primary outcome of nephrotic syndrome ($N = 21$) was significantly poor compared to patients without nephrotic syndrome ($N = 39$). The mean 50% renal survival time of nephrotic patients was 200 ± 29 months ($P = 0.0007$, Fig. 1B). Finally, 10 patients (17%) reached ESRF from 24 to 278 months after the first renal biopsy. Then, 10 patients in ESRF were treated by hemodialysis in 9 patients and renal transplantation in one patient. Six patients died during hemodialysis therapy because of vascular events in 3 patients with APS, and infectious diseases in 3 other patients with lupus activity.

Clinicopathologic findings at the initial renal biopsy and alterations of lupus glomerulonephritis

At initial renal biopsies, 9 patients showed Class I, 10 in Class II, 8 in Class III with 6 of III (A), and 2 of III (A/C). Twenty-three patients were judged as Class IV, including 17 in Class IV-G with 2 of IV-G (A) and 15 of IV-G (A/C), 6 in Class IV-S with one of IV-S (A) and 5 of IV-S (A/C). Both Class IV-S and Class IV-G showed higher scores of activity and chronicity indices ($P < 0.0001$ for AI, $P = 0.0004$ for CI). Ten patients showing mainly subepithelial or intramembranous dense deposits were diagnosed as Class V. There was no Class VI in our series at the initial renal biopsy. When we compared the pathologic diagnoses between two pathologists using

Table 1. Profiles of patients at initial renal biopsies

ISN/RPS 2003 classification	NO.	Age *years*	Sex F:M	u-Prot *g/day*	s-Alb *g/dL*	NS	s-Cr *mg/dL*	CH50 *U/mL*	AI/CI *mean score*
Class I	9	34 ± 6	9:0	0.2 ± 0.1	4.4 ± 0.2	0 (0%)	0.7 ± 0.1	29 ± 2	0.2/0.2
Class II	10	30 ± 4	9:1	0.2 ± 0.1	4.2 ± 0.2	0 (0%)	0.7 ± 0.1	26 ± 3	0.5/0.1
Class III	8 A (6), A/C (2)	35 ± 6	6:2	1.5 ± 0.4	3.6 ± 0.2	1 (13%)	0.7 ± 0.2	24 ± 4	4.5/0.5
Class IV-S	6 A (1), A/C (5)	31 ± 7	5:1	3.9 ± 1.1	3.2 ± 0.4	4 (67%)	1.3 ± 0.2	22 ± 6	5.3/2.0
Class IV-G	17 A (2), A/C (15)	36 ± 2	14:3	3.7 ± 0.5	3.0 ± 0.2	10 (59%)	1.3 ± 0.2	18 ± 3	6.6/3.3
Class V	10	32 ± 4	10:0	3.6 ± 0.7	2.8 ± 0.3	6 (60%)	0.7 ± 0.1	24 ± 2	0.3/0.5
Total	60	33 ± 2	53:7	2.3 ± 0.3	3.5 ± 0.1	21 (35%)	0.9 ± 0.1	23 ± 1	3.2/1.4

Abbreviations are: u-Prot, urinary protein; s-Alb, serum albumin levels; NS, nephrotic syndrome; s-Cr, serum creatinine levels; AI/CI, activity index/chronicity index.

Table 2. Alteration of renal pathology and clinical outcomes

ISN/RPS 2003 classification	Initial no.	Remission/NS or ESRF[a]	Relapse/rebiopsy	Final no.	ESRF/prolonged NS
Class I	9	9 (100%)/0 (0%)	1 relapse → V 8 no rebiopsy	8	0 (0%)/0 (0%)
Class II	10	10 (100%)/0 (0%)	1 relapse → V 9 no rebiopsy	10	0 (0%)/0 (0%)
Class III	8	8 (100%)/0 (0%) (A) 6, (A/C) 2	1 relapse → V 1 follow-up III(A)→III(C) 6 no rebiopsy	7	0 (0%)/0 (0%)
Class IV-S	6	2 (33%)/4 (4[a], 67%) (A/C) 5, (C) 1	1 relapse → IV-G(A/C) 4 follow-up →IV-S(A/C)1,-S(C)1; IV-G(A/C) 1, -G(C) 1 1 no rebiopsy	3	1 (33%)/0 (0%)
Class IV-G	17	11 (65%)/6 (5[a], 29%) (A) 2, (A/C) 15	1 relapse → V 13 follow-up →II 1, IV-G(A/C)11, IV-G(C) 1 3 no rebiopsy	18	8 (44%)/1 (6%)
Class V	10	7 (70%)/3 (1[a], 10%) +II 2, +III(A) 2	1 relapse → V+IV-G(A/C)[b] 4 follow-up → V 3, V+III (A/C) 5 no rebiopsy	14 1	1[b] (7%)/2 (14%)
Total	60	47 (78%)/13(10[a], 17%)	6 rebiopsies at relapse 22 follow-up biopsies	60	10 (17%)/3 (5%)

NS, nephrotic syndrome; ESRF, end-stage renal failure.
[a]Cases with ESRF.
[b]A case of class V + IV-G reached ESRF.

WHO1995 classification and new ISN/RPS2003 classification, there were some discrepancies in class judgments in 10 specimens (17%) by WHO1995 classification, and one specimen (2%) by ISN/RPS2003 classification ($P = 0.0084$ by Fisher exact test).

Patients with Class IV-S, IV-G, or V had massive proteinuria with lower serum albumin levels than those of patients with Class I, II, or III ($P < 0.001$ for proteinuria, $P = 0.003$ for serum albumin). Serum creatinine levels were much higher in patients with Class IV-G or IV-S ($P < 0.005$). Patients with Class IV, especially Class IV-G, also tended to have lower serum complement (CH50) levels ($P = 0.07$, Table 1).

Eight patients changed their histologic classes during follow-up periods. Four patients showing clinical relapse or worsening of proteinuria (each one of Class I, II, III, and IV-G) were diagnosed as Class V at the episodic renal biopsies. Two patients initially diagnosed as Class IV-S (A/C) changed to Class IV-G (A/C) or -G(C) by the follow-up biopsies after 3 to 36 months. One patient, changed from Class V (pure membranous) to Class V+IV-G (A/C), also reached ESRF and died of severe thrombocytopenia and pulmonary infection during her dialysis therapy (Table 2).

There was a significant difference in primary outcome between patients with Class I, II, III, or V, and patients with Class IV-S or IV-G ($N = 23$) at initial biopsy findings (Fig. 2A). Patients with Class IV-S or IV-G at final biopsies showed higher rate of ESRF compared with that of Class I, II, III, or V (40.9% vs. 2.6%, $P < 0.001$, Table 2). The mean 50% renal survival time of Class IV was 189 ± 29 months ($P < 0.0001$ by the Kaplan and Meier life-table method, Fig. 2A). Patients with Class IV-S showed much higher rate of ESRF in 4 out of 6 (67%). There was no statistic difference in primary outcome between Class IV-S and IV-G of initial pathologic diagnosis by the Kaplan and Meier life-table method, however. Patients with Class IV-S tended to have a poorer prognosis (the mean

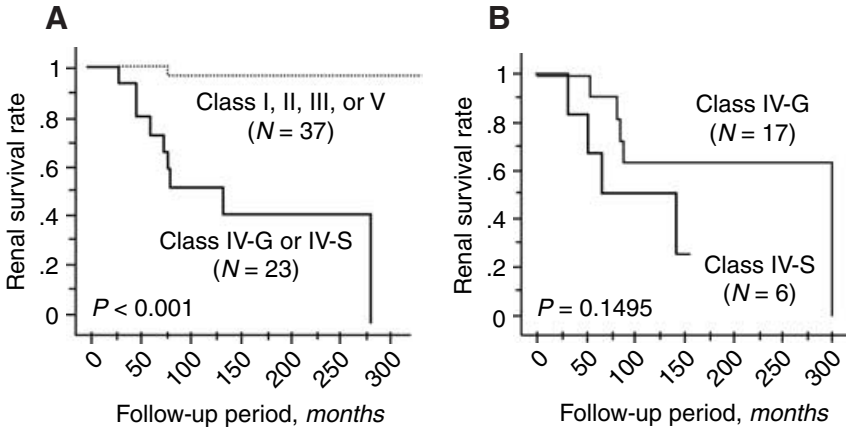

Fig. 2. Different primary outcome of patients with LGN by initial pathologic findings. The group of Class IV-S or IV-G at initial biopsies showed higher rate of ESRF as compared with that of Class I, II, III, or V (40.9% vs. 2.6%) (*A*). The mean time of 50% renal survival in subjects with Class IV-S or -G was 189 ± 29 months ($P < 0.0001$ by the Kaplan and Meier life-table method). There was no statistic difference in primary outcome between Class IV-S and IV-G, however (*B*). The mean times of 50% renal survival in subjects with Class IV-S and -G were 95 ± 22 months and 214 ± 35 months, respectively.

Table 3. Clinicopathologic factors for primary outcome

	Multivariate Cox hazard analysis		
	Hazard ratio	95% CI	*P* value
LGN class IV-S or G	14.82	1.42–155.3	0.025
Nephrotic state (+)	3.39	0.61–18.87	0.163
Activity index	1.10	0.86–1.40	0.437
APS (+)	1.09	0.25–4.65	0.910
Age	0.95	0.88–1.03	0.192
Chronicity index	0.93	0.62–1.40	0.709
	Multivariate stepwise Cox hazard analysis		
	Hazard ratio	chi-square	*P* value
LGN class IV-S or G	25.55	9.42	0.0021

CI, confidence interval, APS, anti-phospholipid syndrome.

Table 4. Clinicopathologic factors for secondary outcome

	Multivariate Cox hazard analysis		
	Hazard ratio	95% CI	*P* value
Nephrotic state (+)	4.03	0.99–16.39	0.051
LGN class IV-S or G	2.15	0.60–7.70	0.241
APS (+)	2.49	0.73–8.49	0.144
Activity index	1.20	1.01–1.44	0.043
Age	0.98	0.92–1.04	0.563
Chronicity index	0.91	0.66–1.25	0.559

Table 5. Clinicopathologic factors for patients' survival

	Multivariate Cox hazard analysis		
	Hazard ratio	95% CI	*P* value
APS(+)	10.87	1.84–63.97	0.0083
LGN class IV-s or G	5.31	0.79–35.74	0.0856
Nephrotic state (+)	3.85	0.60–24.39	0.1555
Activity index	1.28	0.98–1.66	0.0644
Age	1.00	0.92–1.08	0.9680
Chronicity index	0.57	0.33–0.99	0.0495
	Multivariate stepwise Cox hazard analysis		
	Hazard ratio	chi-square	*P* value
APS (+)	5.29	6.07	0.0138
Nephrotic state (+)	3.85	4.14	0.0418

time of 50% renal survival, 95 ± 22 months for IV-S vs. 214 ± 35 months for IV-G, $P = 0.1495$, Fig. 2B).

Clinicopathologic factors for primary and secondary outcomes and patients' survival

In multivariate Cox hazard analysis of the clinicopathologic factors, Class IV (-G or -S) was selected as the most significant risk factor for ESRF by stepwise model (Table 3). In subanalysis for ESRF in Class IV (-S or -G), treatment including methylprednisolone pulse therapy was only selected as a significant improving factor for primary outcome (hazard ratio 5.507, 95% confidence interval 1.128–26.891, $P = 0.0349$). When we did the same analyses by changing the Class IV judgment from new ISN/RPS2003 classification to WHO1995 classification, Class IV was not selected as a risk factor for primary outcome (hazard ratio 2.162, 95% CI 0.146–31.914, $P = 0.5745$), but nephrotic state was significant (hazard ratio 7.353, 95% CI 1.059–50.0, $P = 0.043$).

As for secondary outcome, activity index was the significant risk factor after initial renal biopsies (Table 4). In addition, treatment and proteinuria before therapy were selected as risk factors for secondary outcome in Class IV (-S or -G) (hazard ratio 5.476, 95% CI 1.248–24.019, $P = 0.0242$ for treatment; 13.153, 1.077–160.556, $P = 0.0435$ for proteinuria). Then, as for patients' survival during all follow-up periods, complications with APS or nephrotic syndrome were significant risk factors ($P = 0.0138$, $P = 0.0418$, respectively, Table 5). In this study, 13 patients were diagnosed as APS. Four patients of APS died of arterial thrombosis, 3 hemodialysis patients and in one patient without ESRF. The mean time of 50% survival in patients with APS and LGN was 164 ± 12 months.

DISCUSSION

In order to accommodate the clinicopathologic insights, a new revised classification of LGN was proposed recently [9]. This new classification introduced several important modifications concerning quantitative and/or qualitative difference between Class III, IV, and V

lesions. We have investigated the clinical usefulness of this ISN/RPS 2003 classification to judge the long-term outcome of human LGN in a retrospective study of Japanese.

There were some major discussion points in old 1992 and 1995 WHO classification that there is any difference in the quantitative distribution of segmental lesions between <50%, and more than 50% or not. In other words, some cases with segmental necrosis in more than 50% of glomeruli (category III more than 50%, focal and segmental glomerulonephritis) showed poor prognosis compared to cases with diffuse global endocapillary hypercellularity without necrosis (category IV, diffuse proliferative glomerulonephritis), as reported by Najafi et al [8]. This issue was clearly resolved in the new classification that such cases with severe segmental lesions more than 50% of glomeruli were classed as IV-S. In our analysis, new ISN/RPS 2003 classification was much easier for diagnosis of LGN with little discrepancy in the judgment of classes. Hence, there was a significant difference between new Class III and new Class IV, including both Class IV-G and IV–S. In addition, new Class IV judgment was selected as a significant risk factor for the primary outcome, but not category IV of old WHO 1995 classification. These findings indicated that the new ISN/RPS 2003 classification provided useful information relevant to the long-term renal outcome of human LGN.

As for concern to the difference between Class IV-S (segmental lesions) and Class IV-G (diffuse lesions), there was no statistic difference in renal outcome in this study, suggesting that quantitative (<50% or more than 50%) factor may be important to define the renal outcome. However, the mean time of 50% renal survival in Class IV-S, including focal segmental necrotizing lesions, tended to be shorter than that of Class IV-G. Previous reports pointed out that the focal and segmental glomerular lesions of LGN were characterized by segmental endocapillary proliferation, fibrin deposition, and an intense inflammatory lesion with karyorrhexis, cell wall destruction, and crescents. Moreover, such segmental lesions showing necrosis were similar to the lesions of systemic vasculitis, suggesting a role of cellular immunity in the pathologic process [8, 15]. In addition to quantitative (<50% or more than 50%) factor, qualitative changes (segmental lesions including necrosis) may be an important factor for the renal outcome of human LGN in concern of therapeutic strategies. In the future, a large prospective study may be required to clarify this issue of segmental necrotizing lesions in human LGN.

Another question is how do we deal with or judge the cases of Class V combined with other lesions, or transformed from Class V to other classes such as Class IV. In 1996, Sloan et al [16] reported that membranous glomerulonephritis in patients with SLE (Class Va, pure membranous; Vb, with mesangial hypercellularity; Vc, with segmental endocapillary proliferation and/or necrosis; and Vd with superimposed diffuse endocapillary proliferation in 1982 WHO classification) has a heterogeneous course and outcome, that is, the 10-year actuarial survival rates of Va and b, Vc<50% or Vc more than 50%, and Vd were 72%, 48%, and 20%, respectively, and the differences between these three groups were significant ($P < 0.05$). They concluded that this variability was related to the extent and degree of glomerulonephritis seen on biopsy. Even in our small group analysis, only one out of 10 patients (10%) with Class V at initial renal biopsy reached ESRF because of histologic changes from pure Class V to Class V+ IV-G (A/C). Three other patients with Class V showing prolonged nephrotic state or massive proteinuria over 3 g/day without renal dysfunction had mainly subepithelial or intramembranous lesions even in the follow-up biopsies after 5 to 10 years. All 4 patients of Class V combined with Class II or III entered remission by immunosuppressive therapies. These observations suggested that the renal outcome of Class V was defined by the complicated lesions, especially Class IV-G or IV-S lesions, in spite of membranous lesion itself. Hence, new classification in a combined designation of classes may provide useful pathologic information relevant to clinical treatment and the long-term renal outcome of LGN with Class V.

In multivariate analyses, Class IV-G or -S was only selected as a significant risk factor for primary (renal) outcome, but not activity index or chronicity index. As for activity and chronicity scores, because Austin et al devised a system of applying semiquantitative scores for activity and chronicity by grading and adding the individual morphologic components in a given biopsy as a guide to treatment and prognosis, these scores were used as an adjunct to the WHO classification by many practicing pathologists and clinicians [5–6, 17]. The reproducibility and the predictability of these indices have been questioned by some reports, however [18]. Activity index was a significant risk factor for secondary outcome (patient death and/or ESRF) in our analysis. As we previously reported, activity index related positively with circulating gamma-interferon levels and the degree of glomerular aberrant MHC class II (HLA-DQ) expression [6], and elevated urinary interleukin-8 levels [17]. We speculated that activity index might be reflecting the severity of general condition, especially immunologic disease activities in patients with SLE. Then, the activity index is also a useful clinicopathologic guide to patients' treatment of LGN.

Recently, complication with APS was paid much attention from not only pathologic findings in renal biopsy [19, 20], but also from clinical treatments [21, 22]. As Daugas et al [20] reported, the renal involvement attributing to APS is an independent risk factor over and above LGN that contributes to an elevated prevalence of hypertension, elevated serum creatinine levels, and increased interstitial fibrosis. In this study, APS, as well as nephrotic state, is an independent risk factor for actuarial death

in patients with LGN. Nephrotic syndrome was mainly associated with Class IV (both IV-G and IV-S) or prolonged Class V. Then, these patients with severe proliferative LGN were treated with initial intensive immunosuppressive therapies, followed by maintenance therapy for remission [23, 24], because the initial intensive therapy including methylprednisolone pulse therapy was only a preventing factor to ESRF, as shown in the analysis of Class IV-S or -G in this study. Hence, these therapies increased the incidence of infection in patients with SLE, as we previously reported [25]. These results suggested that the optimal therapy being well balanced between disease activity control, and the advertous effects of immunosuppressive therapy should be considered in the treatment of patients with Class IV or Class V of LGN.

CONCLUSION

We retrospectively analyzed 60 subjects with biopsy proven LGN, and found that new ISN/RPS 2003 classification provided beneficial pathologic information relevant to the long-term renal outcome of LGN and the optimal therapy preventing ESRF and/or death in patients with LGN.

APPENDIX

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