

## Usefulness of ISN/RPS Classification of Lupus Nephritis

About 50-80% of patients with lupus suffer from lupus nephritis which is one of major causes of morbidity and mortality. Renal pathologists and nephrologists should evaluate the degree of histological damages to establish therapeutic plans for lupus nephritis. In order to standardize definitions, to emphasize clinically relevant lesions, and to improve interobserver reproducibility, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification was proposed. Recently, several retrospective validation studies concerning the utility of the ISN/RPS classification, especially among class IV, were performed. In these reports, reproducibility is improved by the definition of diagnostic term, but the outcome related with classification, especially in class IV, is controversial. We performed retrospective analysis of 99 biopsy-proven subjects with lupus nephritis in our facility using the ISN/RPS classification. The class IV-G group tended to exhibit a worse renal outcome, but the difference compared with IV-S was not significant. In a Cox proportional hazards models, Independent histological predictors of poor renal outcome were extracapillary proliferation, glomerular sclerosis and fibrous crescents, while hyaline thrombi and fibrous adhesions were of favorable renal outcome. Both were similarly observed in IV-G and IV-S. The more qualitative categorization by the response to standard treatment may be needed to emphasize clinically relevant lesion related to renal outcome.

Key Words : ISN/RPS Classification; Lupus; Lupus Nephritis; Outcome

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### INTRODUCTION

Systemic lupus erythematosus (SLE) is cryptogenic autoimmune disease, and may give rise to multiple organ damage because of immune complex deposits. The 52,452 patients were registered in Ministry of Health, Labour and Welfare in Japan at the end of 2002. In that registry, the morbidity of SLE is estimated with 8-10 per 100,000 in our country, the ratio of the man and woman is 1:9-10, and the age at onset tends to be 20-40 yr old.

The renal involvement in SLE is so called 'lupus nephritis' and 50-80% of patients with SLE suffer from lupus nephritis. According to the report for The Japanese Society for Dialysis Therapy, the number of patients with SLE who develop end-stage renal failure requiring dialysis is recognized around 300 each year in our country, and lupus nephritis is one of major causes of morbidity and mortality in SLE. The various clinical manifestations are recognized in patients with lupus nephritis, for example, asymptomatic microhematuria, nephrotic syndrome and rapidly progressive glomerulonephritis. It is generally considered that renal biopsy is performed when there are urinary abnormal findings or renal dysfunction and that renal pathologists and nephrologists evaluate the degree

of histological damages to structure therapeutic plans for lupus nephritis.

A new classification was suggested under the support of International Society of Nephrology/Renal Pathology Society (ISN/PRS) in 2003. We will give an outline of this new classification, describe consideration from literature for the new classification, and evaluate the association between the new classification and renal outcome.

The problems for old classifications and the details of new classification

From 1964, the classifications for lupus nephritis have been revised repeatedly regarding identification and definition of various lesions, and a revised WHO classification was proposed in 1982. However, this classification were pointed out many problems; 1) it did not give a definition of quantitative and qualitative evaluation, 2) interobserver reproducibility was not good, 3) the association between histological lesions and clinical findings was open to question, 4) manuscripts using this classification were not submitted. In addition, Najafi et al. (1) reported that segmental necrotic lesions observed in more than 50% of glomeruli in WHO class III were associated with poor

**Table 1.** ISN/RPS 2003 classification of lupus nephritis

I	Minimal mesangial lupus glomerulonephritis (LGN)
II	Mesangial proliferative LGN
III	Focal LGN (<50% of the total number of glomeruli)
	III (A) Purely active: focal proliferative LGN
	III (A/C) Active and chronic
	III (C) Chronic: focal sclerosing LGN
IV	Diffuse segmental (IV-S) or global (IV-G) LGN (50% or more of the total number of glomeruli)
	IV-S (A) or IV-G (A): diffuse segmental or global proliferative LGN
	IV-S (A/C) or IV-G (A/C)
	IV-S (C) or IV-G (C): diffuse segmental or global sclerosing LGN
V	Membranous LGN
VI	Advanced sclerotic LGN (>90% of glomeruli globally sclerosed without residual activity): end stage LGN

**Table 2.** The definition for diagnostic terms

Diffuse: A lesion involving most ( $\geq 50\%$ ) glomeruli
Focal: A lesion involving most (<50%) glomeruli
Global: A lesion involving more than half of the glomerular tuft
Segmental: A lesion involving less than half of the glomerular tuft (i.e. at least half of the glomerular tuft is spared)
Mesangial hypercellularity: At least three mesangial cells per mesangial region in a 3 micron thick section
Endocapillary proliferation: Endocapillary hypercellularity due to increased number of mesangial cells, endothelial cells, and infiltrating monocytes, and causing narrowing of the glomerular capillary lumina
Extracapillary proliferation or cellular crescent: Extracapillary cell proliferation of more than two cell layers occupying one fourth or more of the glomerular capsular circumference
Karyorrhexis: Presence of apoptotic, pyknotic, and fragmented nuclei
Necrosis: A lesion characterized by fragmentation of nuclei disruption of the glomerular basement membrane, often associated with the presence of fibrin-rich material
Hyaline thrombi: Intracapillary eosinophilic material of a homogeneous consistency by which immunofluorescence has been shown to consist of immune deposits
Proportion of involved glomeruli: Intended to indicate the percentage of total glomeruli affected by lupus nephritis, including the glomeruli that are sclerosed due to lupus nephritis, but excluding ischemic glomeruli with inadequate perfusion due to vascular pathology separate from lupus nephritis

renal outcome, and renal outcome in their group was worse than in diffuse proliferative nephritis in WHO class IV.

In 2002, an international group of pathologists, nephrologists, and rheumatologists convened to formulate a new classification of lupus nephritis. In order to standardize definitions, to emphasize clinically relevant lesions, and to improve inter-observer reproducibility, the ISN/RPS 2003 classification was proposed and published in *Kidney International* and *Journal of the American Society of Nephrology* (2, 3).

### ISN/RPS classification

The ISN/RPS classification are given in Table 1, the definition for diagnostic terms are given in Table 2, and the parameters of activity and chronicity are given in Table 3. Overall, it bears a strong similarity to the 1974 WHO classification due to simplicity, but introduces several modifications concerning quantitative and qualitative differences between class III and IV lesions. This classification is based on glomerular pathology, so the significant vascular and tubulointerstitial pathology should be reported as separate entries. The points of ISN/RPS classification are shown below.

**Table 3.** Active and chronic glomerular lesions

Active lesions
Endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction
Karyorrhexis
Fibrinoid necrosis
Rupture of glomerular basement membrane
Crescents, cellular or fibrocellular
Subendothelial deposits identifiable by light microscopy (wireloops)
Intraluminal immune aggregates (hyaline thrombi)
Chronic lesions
Glomerular sclerosis (segmental, global)
Fibrous adhesions
Fibrous crescents

### Class I

It is defined as minimal mesangial lupus nephritis with mesangial accumulation of immune complexes identified by immunofluorescence (or electron microscopy). A complete lack of renal abnormality by light microscopy, immunofluorescence, and electron microscopy (WHO Ia) is excluded from this classification.

**Class II**

It is defined as mesangial proliferative lupus nephritis. The purely mesangial hypercellularity was excluded from parameters of activity in this classification, so the presence of any active or chronic lesions is incompatible with class II.

**Class III**

It is defined as focal lupus nephritis involving less than 50% of all glomeruli. In assessing the extent of the lesions, glomeruli with both active and sclerotic lesions are taken to account. Class III was found to be almost segmental and rarely global in pilot study, so it was not divided into subclasses.

**Class IV**

It is defined as diffuse lupus nephritis involving more than 50% of all glomeruli. This class is subdivided into diffuse segmental lupus nephritis (class IV-S) when >50% of the involved glomeruli have segmental lesions, and diffuse global lupus nephritis (class IV-G) when >50% of the involved glomeruli have global lesions. The rare examples of extensive subendothelial glomerular deposits with almost no proliferation should be included in this category.

In this classification, parameters of activity and chronicity are defined. In the diagnostic line, active lesions (A), active and chronic lesions (A/C), or chronic lesions (C) should be noted.

In assessing the extent of the lesions, both active and chronic lesions will be taken into account.

**Class V**

It is defined as membranous lupus nephritis with global or segmental continuous granular subepithelial deposits (involving >50% of the tuft of >50% of the glomeruli by microscopy or immunofluorescence). When a membranous lesion is associated with the active or chronic lesions of class III or IV, both diagnoses are to be reported in the diagnostic line.

**Class VI**

It is defined as advanced-stage lupus nephritis involving >90% global glomerulosclerosis. There should be no evidence of active lesions.

**Validation studies of ISN/RPS classification of lupus nephritis**

Recently, several retrospective validation studies concerning utility of ISN/RPS classification, especially among class IV, were performed.

Furness et al. (4) reported that a significant improvement in interobserver reproducibility was demonstrated by the new classification and reproducibility of the assessment of disease activity and chronicity remains suboptimal. Hence Groot-scholten et al. (5) showed both ISN/RPS classification and WHO 1995 classification showed low agreement with intraclass correlations coefficients. Although it is difficult to explain this

discrepancy, we sometimes hesitate to diagnose histological findings of glomeruli with both active and chronic change, especially in repeated biopsy specimens. The modifications by treatments or time course may decrease reproducibility.

Yokoyama et al. (6) revealed that class IV in ISN/RPS classification serves as a significant risk factor for the renal outcome, but not category IV in WHO classification. They also showed no statistic difference in renal outcome between Class IV-S and Class IV-G. They pointed out that qualitative changes including necrosis may be important factor for the renal outcome.

Hill et al. (7) also reported no difference in renal outcomes defined as serum creatinine doubling between IV-S and IV-G for 10 yr follow up. Additionally they founded that patients with class IV-G lesions had greater overall immune deposits and subendothelial deposits on IF and greater hyaline deposits on light microscopy, and patients with class IV-S showed predominant mesangial deposits and a much higher rate of glomerular fibrinoid necrosis. They concluded that these lesions may have a different pathogenesis.

Schwartz et al. (8) reported that WHO classification into severe segmental lesions and into diffuse global lesions are not congruent with ISN/RPS IV-S and IV-G. They concluded that the ISN/RPS minimizes pathological and outcome differences between classes IV-S and IV-G which results in the loss of informational content from the renal biopsies. In the ISN/RPS classification, IV-G includes severe chronic lesions such as global glomerulosclerosis and active lesions such as wireloops that may have a good treatment response. These may be reason why no difference related to renal outcome was seen between IV-S and IV-G.

Kim et al. (9) evaluate the response to intravenous cyclophosphamide therapy in patients with class IV-G and class IV-S lupus nephritis patients. They showed higher remission rate in patients with IV-S than patients with IV-G. In this report, the pathological profiles including glomerular sclerosis, cellular crescent and interstitial fibrosis did not differ between IV-G and IV-S. Justly, the IV-S group had predominantly segmental endocapillary proliferation and the IV-G group had predominantly global endocapillary proliferation. The other histological findings (karyorrhexis, fibrinoid necrosis, wireloops, hyaline thrombi, etc) were not shown. Although relationship between each histological findings and treatment response is not evaluated in this report, qualitative varieties between IV-S and IV-G may affect the treatment response or renal prognosis.

Hiramatsu et al. evaluated 92 patients with lupus nephritis according to ISN/RPS classification related with renal outcomes. They found that the renal function was more likely to deteriorate in class IV-G cases than class IV-S cases, but difference was not significant. In subcategorical analysis in IV-G cases, patients with active lesion alone (IV-G [A]) responded well to treatment and patients and renal function of class IV-G (A) cases maintained. Although histological dis-

tributions in IV-G patients were not shown in detail, at least chronic lesions seemed to affect the renal outcomes as said previously (10).

#### Derivation study for histological predictors of renal outcome in our facility

We performed retrospective analysis of 99 biopsy-proven subjects with lupus nephritis in our facility from 1990 to 2006 using the ISN/RPS classification. The prevalence of each category was as follows: class I 3%, class II 13%, class III 9%, class IV-S 20%, class IV-G 46%, class V 8% and class VI 1%. The class IV-G group tended to exhibit a worse renal outcome defined as 1.5 times elevations of creatinine, but the difference was not significant. We evaluated active or chronic findings quantitatively and made the score of each lesions. Among class III, IV-S, and IV-G, endocapillary proliferation score was significantly higher in class IV-G than in class III, and wire-loop lesions were more remarkable in class IV-G than class III and IV-S. The other glomerular scores were similar among each class. Independent histological predictors of poor renal outcome were extracapillary proliferation, glomerular sclerosis and fibrous crescents analyzed by Cox proportional hazards model, while independent histological predictors of favorable renal outcome were hyaline thrombi and fibrous adhesions.

In our study, no statistical difference between IV-S and IV-G were found as both favorable and poor renal outcome predictors. Several limitations of this study should be noted. In this study, only 14 patients reached the primary endpoint.

### CONCLUSION

We reviewed essence of ISN/RPS classification of lupus nephritis and recent validation study related with classification. The interobserver reproducibility was improved in this classification mostly. The more qualitative categorization by the response to standard treatment may be needed to emphasize clinically relevant lesion related to renal outcome.

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