

Significance of global versus segmental subclassification of class III and IV lupus nephritis: a single center experience

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ABSTRACT

Introduction: Class III and IV are the most ominous among the classes of lupus nephritis (LN) and there are contradictory reports on whether LN class IV-G (global) differs from LN class IV-S (segmental), as envisaged by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003 classification. These subcategories are not validated for LN class III. This study was designed to assess the differences between global and segmental subclasses in classes III and IV of LN.

Patients and Methods: In a retrospective analysis, the kidney biopsies of 84 patients with new-onset LN were analyzed. The Student's t-test and Mann-Whitney test were employed to compare differences between the means of continuous variables among the two groups. Fisher's exact test was used to compare the categorical variables. A *p*-value <0.05 was considered statistically significant.

Results: Of 84 patients, 69 (82.1%) were females and 15 (17.9%) males, with the female to male ratio of 4.6:1. The mean age of all patients was 32.7±12.6 years. The mean serum creatinine at the time of biopsy was 1.5±0.94 mg/dl (range: 0.7 to 5 mg/dl) and the mean urinary protein excretion was 1.6±1.9 g/day. Among 84 biopsies, 26(30.95%) were classified as class III and 37 (44.05%) to class IV LN. In class IV LN, serum creatinine was significantly higher in global versus segmental subcategory (2.4±1 vs. 1.1±0.5 mg/dl; *p*=0.034), while 24-h proteinuria was not significantly different between the subcategories (2.7±1.2 vs. 3.1±1.0 g/d, *p*=0.56). In LN class III, the mean age, serum creatinine and 24-hour proteinuria did not show significant differences

between the global and segmental subcategories (37±17 vs. 30±15 years, *p*=0.58; 1.2±0.2 vs. 1.25±0.6 mg/dl, *p*=0.66; 2.03±0.5 vs. 3.1±3.5 g/day, *p*=0.45, respectively). The proportion of glomeruli showing endocapillary proliferation was significantly higher in global than in segmental subclasses (94.25% vs. 5.72; *p*=0.026) in class IV LN. The activity and chronicity percent also revealed higher values in global subclass vs. segmental subclass of class IV LN (*p*=0.038 and *p*=0.045, respectively). These parameters were not significantly different among the global and segmental subcategories of class III LN (*p*>0.5 for all parameters).

Conclusion: In conclusion, our study showed significant differences in renal function and some pathological features on renal biopsies among the global and segmental subclasses of class IV LN. There were no significant differences among these subclasses of class III LN. Further, and larger studies are needed on this subject to substantiate the above results.

Keywords: Focal and global lupus nephritis; Lupus pathology; ISN/RPS classification.

INTRODUCTION

The International Society of Nephrology and Renal Pathology Society (ISN/RPS), proposed a new classification for lupus nephritis (LN) in 2003¹. The proposed changes sought to improve inter-observer agreement and reproducibility and to eliminate the ambiguities seen with prior classifications²⁻⁵. The most significant change in the new classification is undoubtedly the subdivision of class IV LN¹. Diffuse endocapillary or extracapillary glomerulonephritis involving 50% of all glomeruli or more (described as class IV) is divided into two subcategories: global and segmental^{1, 6-11}. Diffuse global LN (class IV-G) is identified when the lesions in-

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involve more than 50% of the glomerular tuft, whereas, diffuse segmental LN (IV-S) is defined when at least 50% of the involved glomeruli exhibit lesions involving less than half of the glomerular tuft^{1,2,10}. Additionally, both subcategories are scored also for active and chronic lesions. In fact, after the presentation of the ISN/RPS classification, comparisons between LN subclasses IV-S and IV-G became a matter of dispute^{1,2,10}. While the two subclasses revealed distinct clinical and morphologic characteristics at baseline, some studies showed that the outcome did not vary significantly. Additionally, on repeat biopsies, transitions from IV-G to IV-S or converse were detected. This finding may indicate a similar pathogenesis for these two forms. Various subsequent investigators tried to show better outcome or better response to cyclophosphamide induction therapy in LN class IV-S than in IV-G¹¹⁻¹⁷. However, the recently reported studies were conducted in relatively small groups of patients who did not consistently receive similar therapies^{10,12,17}. Given that, there are few studies currently available concerning the association of demographic, clinical, and morphologic lesions of segmental and global subclasses of classes III and IV LN, and whilst the conclusions of various investigations are contradictory, our current study sought to analyze the existing evidence on the differences between these subcategories in classes III and IV of LN.

PATIENTS AND METHODS

STUDY AND SETTING

The present study is a retrospective analysis of kidney biopsies of 84 patients with new-onset LN, who were referred by either rheumatologists or nephrologists. The patients fulfilled the revised American College of Rheumatology (ACR) criteria for systemic lupus nephritis (SLE)¹⁸ as defined by their physicians. Only those patients were included in whom no pre-biopsy treatment was given. Kidney biopsies were reported according to the 2003 ISN/RPS classification for LN¹. The study was performed from January 2008 to January 2014. All performed kidney biopsies were referred to a single nephropathology laboratory. The kidney morphologic lesions were reviewed by a single nephropathologist.

CHARACTERIZATION OF LN

The definitive diagnosis of LN was based on clinical

and laboratory data and finally by immunofluorescence (IF) study which included significant positive C1q (more than 2+ intensity) accompanied by IgG, IgA, IgM and C3 deposits (full-house pattern), which were semi-quantitatively graded from zero to 3+ according to the intensity of fluorescence^{19,20}. Morphologic lesions were assessed as specified by the ISN/RPS 2003 LN classification by light microscopy (LM)^{1,7,12}.

DEFINITION OF MORPHOLOGIC VARIABLES

The morphological assessment of the LM was recorded according to the ISN/RPS 2003 histological definition of classes of LN^{1,7,12}. Renal biopsies containing <10 glomeruli were excluded. Class III (focal LN) was characterized as focal glomerulonephritis involving less than 50% of all glomeruli, whereas, class IV LN as diffuse glomerulonephritis involving $\geq 50\%$ of total number of glomeruli, either with global (class IV-G) or segmental (class IV-S) involvement, and also with percent of active or chronic lesions^{1,7,12}. Diffuse segmental proliferative LN (IV-S) was designated when at least 50% of the involved glomeruli showed lesions involving less than half of the glomerular tuft. Diffuse global LN (IV-G) was diagnosed when the lesions affected more than 50% of the glomerular tuft^{1,7,12}. The activity and chronicity was assessed as the proportion (percentage) of glomeruli showing active lesions, rather than the National Institutes of Health (NIH) activity and chronicity indices.

DEMOGRAPHICS AND LABORATORY DATA

We obtained the patients' demographic and laboratory data at the time of their biopsies, as well as the pathological variables on renal biopsies, from a review of their original renal biopsy request forms.

ETHICAL ISSUES

(1) The research followed the tenets of the Declaration of Helsinki; (2) informed consent was obtained; (3) the research was approved by the institutional review board.

STATISTICAL ANALYSIS

All continuous values are expressed as mean \pm standard deviation (SD) and categorical variables as numbers and percentages. Normality assumption was checked for continuous variables and student's t-test and Mann-Whitney tests were employed as appropriate to compare the differences between the means of continuous variables among the groups. Fisher's exact test was used to compare the categorical variables

among the groups. Data were analyzed by Stata software (Stata Corp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: Stata Corp LP). A *p*-values of less than 0.05 was assumed to be significant.

RESULTS

In our observational study, we enrolled a total of 84 LN patients' biopsies. All patients were of Iranian origin and racially homogeneous. Of 84 patients, 69 (82.1%) were females and 15 (17.9%) males, with a female to male ratio of 4.6:1. The mean age of all patients was 32.7 ± 12.6 years. The mean serum creatinine at the time of biopsy was 1.5 ± 0.94 mg/dl and the mean 24-hour proteinuria was 1.6 ± 1.9 g.

Among 84 patients, 63 (75%) belonged to the proliferative LN classes III (26; 30.95%) and IV (37; 44.05%). Table I illustrates the frequency distribution of LN classes III and IV and their subclassification according to the global and segmental subcategories. These two classes of LN formed the basis for further statistical analysis regarding the differences between global and segmental subcategories of glomerular involvement in LN. Tables II and III illustrate the differences in demographic, laboratory, and pathological parameters at the time of renal biopsies among the

global and segmental subclasses of class III and IV LN cases.

The vast majority of cases of LN class III showed segmental glomerular involvement (20/26; 76.9%), while in LN class IV, global involvement was much more common (34/37; 91.9%).

In class III LN, there was no significant difference in the mean age, mean serum creatinine, the amount of proteinuria or the pathological features on renal biopsy among the global and segmental subcategories (all parameters; $p > 0.5$), as shown in Table II.

In class IV LN, there was a significant difference in the mean serum creatinine between global and segmental subcategories (2.4 ± 1 vs. 1.1 ± 0.5 mg/dl; $p = 0.034$), while proteinuria showed no significant difference ($p = 0.56$). The proportion of endocapillary proliferation showed significant difference between global and segmental subclasses (0.94 vs. 0.56 ; $p = 0.026$) of class IV LN. Analysis of the activity and chronicity percent revealed higher values of both activity ($p = 0.038$) and chronicity percent ($p = 0.045$) in global subclass vs. segmental subclass.

However, there was no significant difference in mean age, amount of proteinuria, proportion of totally sclerotic glomeruli and proportion of crescents between the subclasses of global and segmental lesions ($p > 0.5$).

An analysis of all patients of classes III and IV LN re-

TABLE I. THE FREQUENCY DISTRIBUTION OF LUPUS NEPHRITIS INTO CLASSES III AND IV AND GLOBAL AND SEGMENTAL SUBCATEGORIES

Classification	Total patients		Global		Segmental	
	Number	Percent	Number	Percent	Number	Percent
Class III	26	30.95	6	23.07	20	76.92
Class IV	37	44.04	34	91.89	3	8.1
Total	63	75	40	63.5	23	36.5

TABLE II. A COMPARISON OF THE PATIENTS' DATA IN CLASS III LUPUS NEPHRITIS ACCORDING TO THE GLOBAL AND SEGMENTAL SUBCATEGORIES AT THE TIME OF RENAL BIOPSY

Parameters	Total n=26	Global n=6	Segmental n=20	p. Value
Age, mean \pm SD (years)	30.7 ± 15.25	34 ± 17	30 ± 15	0.589
Creatinine, mean \pm SD (mg/dl)	1.2 ± 0.56	1.2 ± 0.2	1.25 ± 0.6	0.669
Proteinuria/day, mean \pm SD (g)	2.8 ± 2.9	2.032 ± 0.5	3.1 ± 3.5	0.455
Activity, mean \pm SD (%)	30 ± 23.34	36.3 ± 29	27.6 ± 20	0.418
Chronicity, mean \pm SD (%)	8.3 ± 10.05	10 ± 12	8.6 ± 9.7	0.775
Proportion of endocapillary proliferation, n (%)	20 (76.9)	5 (25)	15 (75)	0.671

TABLE III. A COMPARISON OF THE PATIENTS' DATA IN CLASS IV LUPUS NEPHRITIS ACCORDING TO THE GLOBAL AND SEGMENTAL SUBCATEGORIES AT THE TIME OF RENAL BIOPSY

Parameters	Total n=37	Global n=34	Segmental n=3	p. Value
Age, mean±SD (years)	32.8 ± 12.2	33.2 ± 12	27.6 ± 2	0.431
Creatinine, mean±SD (mg/dl)	2.1 ± 1.09	2.4 ± 1	1.1 ± 0.5	0.034
Proteinuria/day, mean±SD (g)	2.7 ± 1.2	2.7 ± 1.2	3.1 ± 1.04	0.563
Activity, mean±SD (%)	64.16 ± 28.62	68.4 ± 26	35 ± 21.7	0.038
Chronicity, mean±SD (%)	17.9 ± 21.37	16.2 ± 10	30.6 ± 25	0.045
Proportion of endocapillary proliferation, n (%)	35 (94.6)	33 (94.28)	2 (5.72)	0.026

TABLE IV. THE MAIN CHARACTERISTICS OF PATIENTS ACCORDING TO THE GLOBAL AND SEGMENTAL SUBCLASSES OF CLASS III AND IV LUPUS NEPHRITIS AT THE TIME OF BIOPSY.

Parameters	Total n=63	Global n=40	Segmental n=23	p. Value
Age, mean ± SD (years)	31.98 ± 13.47	33.25 ± 13.23	29.95 ± 13.83	0.35
Creatinine, mean ± SD (mg/dl)	1.7 ± 1.01	1.98 ± 1.1	1.3 ± 0.69	0.01
Proteinuria/day, mean ± SD (g)	2.7 ± 2.1	2.6.9 ± 1.2	3.1 ± 3.1	0.35
Activity, mean ± SD (%)	50 ± 31	61.92 ± 30.36	26.82 ± 19.94	<0.001
Chronicity, mean ± SD (%)	13.95 ± 18.13	14.87 ± 19.21	12.35 ± 16.36	0.60
Proportion of endocapillary proliferation, n (%)	55 (87.3)	37 (68.51)	17 (31.48)	0.042

vealed higher values of serum creatinine (1.98 ± 1.1 vs. 1.3 ± 0.69 mg/dl; $p=0.01$) in global subclass than segmental subcategory. The proteinuria was not significantly different between the two subcategories (2.6 ± 1.2 vs. 3.1 ± 3.1 g/day; $p=0.35$). There was a significant difference of active lesions (61.92 ± 30.36 vs. $26.82 \pm 19.94\%$; $p<0.001$) with higher values observed in the global subclass, while there was no significant difference of chronic lesions between the two subclasses ($p=0.60$). In this study, we also detected a higher value of endocapillary proliferation ($p=0.04$) and extracapillary proliferation ($p=0.03$) in global subclass in comparison to segmental subclass. Table IV summarizes the comparisons between the global and segmental subcategories of all patients of classes III and IV LN.

Figure 1 shows some representative lesions of classes III and IV segmental and global lesions.

DISCUSSION

The ISN/RPS 2003 classification of LN is getting widespread acceptance and seems to be achieving its goals of reproducibility and clinical relevance^{1,7,12}. A number of innovations were sought in the formulation

of this classification. In particular, class IV LN was subclassified into segmental or global subclasses according to the proportion of the capillary tuft involvement. The distinction between IV-S and IV-G may have significant implications for differences in the pathogenesis and outcome^{1,7,12}. There is still controversy as to whether kidney outcomes differ between the global and segmental subclasses of class IV LN (diffuse proliferative LN)^{7,12}. Indeed, various retrospective investigations have revealed significant clinical and morphological differences between IV-G and IV-S, however, no significant differences in the outcome have been detected yet^{7,12}.

In this study, no significant differences of the analyzed parameters were found among the global and segmental subclasses of LN class III. This is not surprising given the lack of validation of this subdivision in LN class III. Thus, our results add further evidence to this observation. However, as shown in Table I, there were very few cases of global glomerular involvement in LN class III. This marked skewness of the cases in favor of segmental involvement in LN class III may partly be responsible for the lack of statistical significance of the results.

Among the class IV LN subcategories, serum creatinine, proportion of endocapillary proliferation and

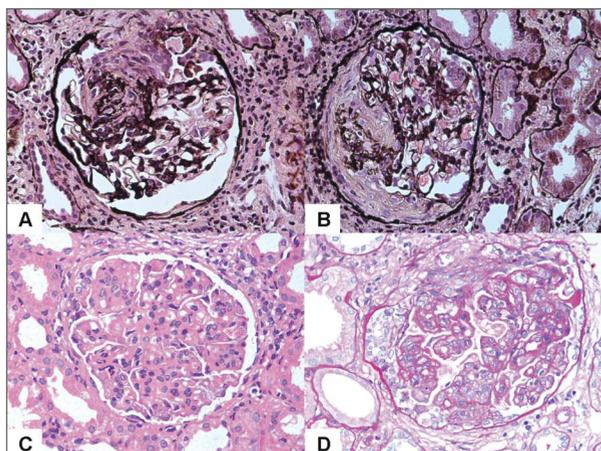


FIGURE 1. Morphological appearances of different classes of lupus nephritis. Each of these lesions may be seen in lupus class III and IV nephritis, but segmental lesions are common in class III and global in class IV. A) Medium-power view of a glomerulus showing segmental necrotizing lesion with focal crescent formation. Classified as a segmental and active lesion (Silver stain, $\times 200$). B) Another glomerulus from the same biopsy showing segmental sclerosing lesion. Classified as a chronic lesion. (Silver stain, $\times 200$). C) A glomerulus showing global or diffuse proliferative lesion of the mesangiocapillary type. A tiny crescent is seen at 10 o'clock position. (Hematoxylin and eosin stain, $\times 200$). D) Another glomerulus showing diffuse or global proliferation and crescent formation. (Periodic acid-Schiff stain, $\times 200$)

the activity and chronicity percent were significantly higher in the global subcategory. Other parameters did not show significant differences among the two subcategories. One possible reason for this may also be the very few cases of segmental involvement in class IV LN. Because of the markedly skewed distribution of the global and segmental cases in LN classes III and IV, we also analyzed all the parameters among all the global and segmental subcategories of combined classes III and IV LN. On doing this, we observed significant differences in the serum creatinine, activity percent and proportion of endocapillary proliferation. The other parameters did not show significant differences, as shown in Table IV.

To assess the differences between LN class IV-G and IV-S in Koreans and focus on the response to cyclophosphamide induction treatment, Kim *et al.*, studied 52 patients with biopsy-proven diffuse LN, who had been treated with intravenous (I/V) cyclophosphamide over a 10-year period²². Of the 42 patients evaluated, 71% had IV-G and 29% had IV-S. They found that pre-treatment 24-hour urinary protein was

significantly higher in IV-G than in IV-S individuals. Following induction therapy, complete remission rates were significantly higher in individuals with IV-S than in patients with IV-G of LN. They concluded that, class IV-G of LN responded more poorly to induction therapy with I/V cyclophosphamide pulse than class IV-S of LN²². In contrast to the above study, 24-hour proteinuria was not significantly different among IV-G and IV-S in our study. This may be partly due to the fact that the number of IV-S cases was very low (8.1%) in our study. Moreover, we also did not analyze the treatment or the response to therapeutic intervention in the present study.

To evaluate whether the different ISN/RPS classes of LN have a distinct baseline presentation, short-term response to immunosuppression and long-term prognosis, Vandepapelière *et al.*, studied 98 patients with new-onset LN²³. At baseline, serum creatinine and 24-hour proteinuria were higher in class IV-G, and the activity index on kidney biopsy in class IV-S and IV-G compared to class III. They found that poor outcomes did not differ significantly between the groups, although there was a trend toward more kidney impairment at follow-up in class IV-G compared to classes IV-S and III. They interpreted that subclassifying proliferative LN into classes III, IV-S and IV-G offers less clinically discriminant prognostic information than baseline chronicity index²³. This may be due to the availability and the use of very potent drugs for proliferative LN, which control the active lesions rather than the chronic lesions. To assess the differences between IV-G and IV-S of LN in a Chinese population with LN, a total of 172 cases of SLE were classified as class IV LN, including 152 cases with IV-G and 20 cases with IV-S. Lower serum creatinine in IV-S was detected²⁴. The results from our study support this finding. On pathological evaluation, the score of endocapillary hypercellularity, and total activity indices were significantly lower in IV-S. We also found similar results for these parameters. Yu *et al.*, concluded that there are significant differences in the clinical and pathological manifestations between IV-S and IV-G LN which need further investigation²⁴.

To evaluate the use of the ISN/RPS LN classification and the role of repeated renal biopsy in routine clinical practice, 142 patients with LN were investigated by Pagni *et al.*²⁵. Their study showed that the serum creatinine, proteinuria, blood pressure levels and histological classes were more severe in class IV-G, both at first and repeated renal biopsy²⁵. They concluded that, mor-

phological differences between segmental and global forms do exist, perhaps due to different pathogenetic mechanisms²⁵. Similarly, Gao *et al.*, detected that class IV-G had more severe hypertension and higher scores of interstitial fibrosis, glomerular active lesions, tubular and vascular lesions. Class IV-S had a higher percentage of glomerular fibrinoid necrosis. Class IV-S appeared to have a higher rate of transformation to class II than class IV-G²⁶. To evaluate the association of active and chronic lesions with kidney outcome according to the ISN/RPS classification in patients with LN, Kojo *et al.*, conducted an investigation on 99 biopsy-proven subjects with LN. They observed a worse renal outcome of IV-G group compared with the IV-S group; however, the difference was not statistically significant^{27, 28}. Unfortunately, we were not able to analyze the renal outcome in our current study.

LIMITATIONS IN THE STUDY

There are a number of limitations to the current study. The study is retrospective in nature and originates from a single center. The biopsies were evaluated by a single nephrologist, which, although ensured consistency of the findings, remains a weakness of the study. There is also no information on the treatment and most importantly, on the outcome of the cohort. We are actively following this cohort and will share our experience on these aspects in near future²⁸. The numbers of global and segmental cases are also markedly skewed in classes III and IV LN and this may account for the non-significant results in the current study. A large study with more cases of both subclasses in both classes of LN is needed to clarify these results.

CONCLUSION

In conclusion, the results from our study showed significant differences in renal function and some pathological features on renal biopsies among the global and segmental subclasses of class IV LN. There were no significant differences among these subclasses of class III LN. Further, and larger studies are needed on this subject to substantiate the above results.

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