The ISN/RPS 2003 classification of lupus nephritis: An assessment at 3 years

GS Markowitz[1] and VD D'Agati[1]

[1]*Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York, USA*

The 2003 International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Classification of lupus nephritis (LN) was designed to eliminate ambiguities and standardize definitions. Major changes from the 1982 Modified WHO Classification include the elimination of the normal biopsy category and the subcategories of membranous Class V, the introduction of sharper distinctions between the classes, and the addition of subcategories within diffuse LN (class IV) for predominantly segmental (LN IV-S) and global (LN IV-G) lesions. It stipulates that sclerotic glomeruli owing to scarred LN should be taken into account when assessing the percentage of glomeruli affected by LN. Since its publication, the ISN/RPS classification has been used successfully in a number of clinical-pathologic studies. Several studies addressing the relationship between LN IV-S and LN IV-G have failed to identify a significantly worse outcome in IV-S than IV-G, although there were some differences in presenting clinical and pathologic features. Importantly, the ISN/RPS classification has achieved its goal of improved interobserver reproducibility. Its use has increased the percentage of LN biopsies meeting criteria for class IV. As it gains widespread acceptance, the ISN/RPS classification is already providing a standardized approach to renal biopsy interpretation needed to compare outcome data across centers.

Kidney International (2007) **71,** 491–495. doi:10.1038/sj.ki.5002118; published online 31 January 2007

KEYWORDS: lupus nephritis; ISN/RPS classification

Correspondence: *GS Markowitz, Department of Pathology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, VC14-224, New York, New York 10032, USA. E-mail: gsm17@columbia.edu*

Received 26 October 2006; revised 6 December 2006; accepted 12 December 2006; published online 31 January 2007

In May of 2002, an international group of 23 individuals including pathologists, nephrologists, and rheumatologists convened at Columbia University in New York, New York to develop a revised classification of lupus nephritis (LN). Working under the auspices of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS), the group aimed to 'accommodate the clinicopathologic and pathogenetic insights that have accumulated since the 1982 and 1995 modifications of the original 1974 WHO classification and to eliminate inconsistencies and ambiguities'. The meeting was spurred by a widely perceived need to re-examine existing classifications, provide clearer definitions and distinctions between the classes, and improve reproducibility and interobserver agreement. As a testament to the importance of this document in the international renal community, the ISN/RPS 2003 classification of LN was published simultaneously in *Kidney International* and the *Journal of the American Society of Nephrology* in February 2004[1,2] (Table 1).

ISN/RPS 2003 CLASSIFICATION OF LN: SUMMARY OF CHANGES

The group set out to use definitions that would be workable wherever renal pathology is practiced in the world. Because many centers outside the US routinely use light microscopy (LM) and immunofluorescence (IF), but may not have access to electron microscopy, the definitions chosen reflect that bias. The working group was unanimous in its decision to eliminate a 'normal' renal biopsy from the classification of LN, both because this situation is rare in clinical practice and because it is a fundamental contradiction in terms to refer to a normal biopsy as a manifestation of disease. Instead, it substituted the mildest possible form of LN for class I. Termed 'minimal mesangial LN', class I is defined as normal appearing glomeruli by LM with immune deposits confined to the mesangium by IF. Class II, 'mesangial LN', is defined by mesangial proliferation by LM and mesangial deposits by IF. Because no studies have shown a difference in prognosis between cases with mild, moderate, or severe mesangial proliferation, class II includes mesangial proliferation of any degree. Class II allows for the existence of a rare minute subendothelial or subepithelial deposit visible by IF or electron microscopy, but not by LM. This accommodation was made because of the general experience among renal

pathologists that this situation is not unusual and should not be overinterpreted as a higher lesion. On the other hand, subendothelial deposits that are visible by LM without endocapillary proliferation are incompatible with class II and should be diagnosed as class III or IV depending on their distribution in $>$ or $<50\%$ of glomeruli. A subtle but important change in the ISN/RPS classification is to substitute the term 'focal LN' for 'focal proliferative LN'; similarly 'diffuse LN' replaces 'diffuse proliferative LN'. This refinement was introduced to reflect the heterogeneous phenotype of the class III and IV lesions, which do not always manifest classical endocapillary proliferation. It allows for a variety of endocapillary and extracapillary changes, including membranoproliferative features without luminal closure, subendothelial deposits visible by LM without endocapillary proliferation, and crescents without endocapillary proliferation. The distinction between class III and IV is defined precisely as $<50\%$ of glomeruli exhibiting such endocapillary or extracapillary lesions in class III and $\geqslant 50\%$ in class IV. For class III, the focal lesions may be segmental or global. For class IV, subcategories were added depending on whether the majority ($\geqslant 50\%$) of lesions were segmental (designated as IV-S) or global (designated as IV-G) (Figure 1). Instead of using numbered or lettered subcategories for active and chronic lesions, the ISN/RPS classification affixes a simple mnemonic (A) for purely active lesions, (C) for purely chronic lesions, and (A/C) for any combination of active and chronic lesions.[3,4]

In the 1982 WHO classification of LN, class V (membranous LN) contained subcategories to describe the overlap of class V with Class II (Vb), III (Vc), or IV (Vd). This placed undue emphasis on the membranous lesion at the expense of the more dangerous proliferative lesion, creating the potential for serious miscommunications.[3] In the ISN/RPS classification, these subcategories have been eliminated such that a biopsy with features of both diffuse LN and membranous LN is accorded separate diagnoses of class IV and class V in the diagnostic line. For the first time a threshold for the diagnosis of membranous LN (class V) in the setting of focal or diffuse LN has been defined. An additional diagnosis of membranous LN class V is made when subepithelial deposits involve $\geqslant 50\%$ of the glomerular tuft in $\geqslant 50\%$ of glomeruli. This simple rule of $\geqslant 50\%$ (indicating involvement of the majority of glomeruli) is a recurring motif throughout the ISN/RPS classification that is both logical and easy to remember. Finally, LN class VI ('advanced sclerosing LN') is now more clearly defined, requiring that $>90\%$ of glomeruli be globally sclerotic with no evidence of ongoing activity.

The ISN/RPS classification sets down a simple, but important, stipulation that may seem obvious. It requires that the diagnostic line of the report include entries for the attendant tubulointerstitial and vascular lesions. Tubular atrophy, interstitial fibrosis, inflammation, and forms of arteriopathy should be separately enumerated and graded. Because the classification covers only immune complex-mediated forms of glomerulonephritis, separate diagnoses should be entered for other pathologic processes, such as thrombotic microangiopathy or forms of podocytopathy

Table 1 | ISN/RPS (2003) classification of LN

Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN* ($<50\%$ of glomeruli)
	III (A): active lesions
	III (A/C): active and chronic lesions
	III (C): chronic lesions
Class IV	Diffuse LN* ($\geqslant 50\%$ of glomeruli)
	Diffuse segmental (IV-S) or global (IV-G) LN
	IV (A): active lesions
	IV (A/C): active and chronic lesions
	IV (C): chronic lesions
Class V	Membranous LN
Class VI	Advanced sclerosing LN ($\geqslant 90\%$ globally sclerosed glomeruli without residual activity)

LN, lupus nephritis.
*Indicate the proportion of glomeruli with active and with sclerotic lesions.
*Indicate the proportion of glomeruli with fibrinoid necrosis and with cellular crescents.
*Indicate and grade (mild, moderate, and severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis, or other vascular lesions.
*Class V may occur in combination with III or IV in which case both will be diagnosed.

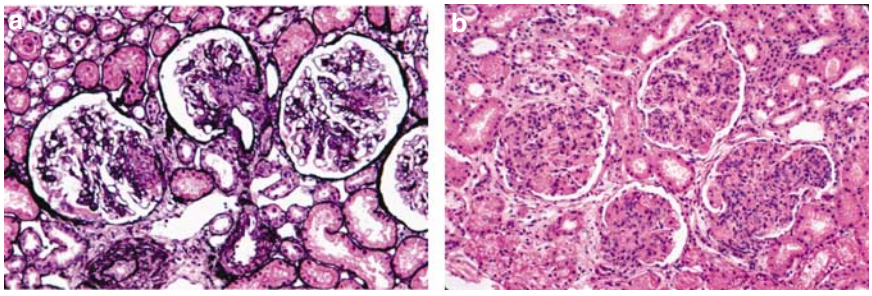

Figure 1 | Diffuse LN (class IV). (**a**) Low power views showing diffuse segmental and (**b**) diffuse global endocapillary proliferative glomerulonephritis, typical of LN class IV-S and IV-G, respectively. (**a**) Jones methenamine silver at original magnification $\times 100$ and (**b**) hematoxylin and eosin at original magnification $\times 100$.

(such as minimal change disease or collapsing focal segmental glomerulosclerosis).[5,6] Although self-evident, the importance of these practical guidelines to biopsy reporting cannot be underestimated.

LN CLASS IV-S VS IV-G: 'TO BE OR NOT TO BE'

Undoubtedly the most controversial aspect of the ISN/RPS 2003 classification is the introduction of a subclassification within diffuse LN (class IV) for biopsies with predominantly segmental ('IV-S') or global ('IV-G') distribution of lesions. Although intuitively one might think that global endocapillary lesions (IV-G) carry a worse prognosis, this is not necessarily so.[7] The Lupus Nephritis Collaborative Study Group performed a prospective study on 'severe LN' that included 24 patients who met modern criteria for LN IV-S and 35 patients who met criteria for LN IV-G.[7] Both groups were similar with respect to baseline clinical and serologic parameters. On renal biopsy, LN IV-S had more segmental endocapillary proliferation and fibrinoid necrosis. In contrast, LN IV-G was more commonly associated with large subendothelial 'wire loop' deposits and intracapillary deposits ('hyaline thrombi'), suggesting higher immune complex load. Patients with LN IV-S had lower activity and higher chronicity indices, although the differences did not reach statistical significance. The two groups received similar treatment including prednisone, cyclophosphamide, and in some cases plasmapheresis. The 5-year cumulative remission rate was 73% for patients with LN IV-G vs 48% for LN IV-S ($P<0.05$). Renal survival at 10 years was 75% for LN IV-G vs 52% for LN IV-S ($P<0.05$). The authors concluded that biopsies with segmental endocapillary proliferation involving $>50\%$ of glomeruli (which they had called 'class III $>50\%$', now termed IV-S) should be included within class IV, appear to have a worse prognosis than biopsies with diffuse endocapillary proliferation (LN IV-G), and may require more aggressive therapy. The authors speculated that different pathogenetic mechanisms may be operant in this group, which exhibits significantly less immune complex deposition than IV-G, resembling a 'pauci-immune' GN. Potential roles for anti-neutrophil antibody, anti-endothelial antibody, and anticardiolipin antibody have been proposed, but none of these have been studied systematically. This study suggested that these subgroups are qualitatively different, such that LN IV-S and LN IV-G do not represent a simple continuum of disease.[7] The distinction between LN IV-S and IV-G was incorporated in the ISN/RPS 2003 classification to allow multiple centers in different parts of the world to examine this issue.

SCLEROTIC GLOMERULI: STAND UP AND BE COUNTED

Another major emphasis in the ISN/RPS 2003 classification of LN is the handling of sclerotic glomeruli. The previous classification systems for LN did not specifically address this issue, leading to major differences in practice among renal pathologists. Some renal pathologists would ignore sclerotic glomeruli when determining the percentage of glomeruli affected by LN whereas others factored both scarred and nonsclerotic glomeruli into the equation. According to the ISN/RPS system, both active and chronic scarred glomeruli must be taken into account. Thus, 'global or segmental glomerular scars that are interpreted as the chronic sequela of previous glomerular endocapillary proliferation, necrosis, or crescents must be considered manifestations of focal or diffuse LN and should be included in a count of total glomeruli affected. Wherever possible, however, glomeruli with ischemic obsolescence (as frequently observed in the subcapsular cortex) should be excluded. The classification also allows for class V to develop lesions of segmental or global sclerosis as it evolves to chronicity, without necessarily implying transformation to a proliferative class. Thus not all sclerosing lesions carry the same implications and the pathologist should use whatever clues are available to determine by what route a glomerulus may have become sclerotic. Understandably, this may not always be possible without vision of hindsight. If renal pathologists assume that any globally sclerotic glomeruli found in a biopsy from a young adult with systemic lupus erythematosus is the sequela of a previous proliferative lesion, the number of biopsies diagnosed as class III or IV will necessarily increase.[8]

ACTIVITY AND CHRONICITY: DO WE NEED AN INDEX?

In the ISN/RPS 2003 classification of LN, the renal pathologist should indicate the proportion of glomeruli with active and chronic lesions in the diagnostic line of the biopsy report. In particular the proportion of glomeruli with fibrinoid necrosis and cellular crescents should be specified. In this way, important information about activity and chronicity is recorded regardless of whether the pathologist uses a formal activity and chronicity index. A list of which lesions meet criteria for active and chronic lesions was clearly set forth by the working group.[1,2] Pathologists are encouraged, but not required, to supplement their reports with an activity or chronicity index, such as the National Institute of Health scoring system or another index of their choice.[9] At Columbia University, we have used the National Institute of Health scoring system for 2 decades; we have found that this information is useful to our clinicians and its inclusion is generally appreciated, particularly when comparing changes over time in repeat biopsies from individual patients. Of course, more important than the actual numerical score for total activity and chronicity is the microscopic description of the various components of activity and chronicity, because the presence of such active features as subendothelial deposits or interstitial inflammation are generally regarded as more reversible with therapy than such ominous lesions as cellular crescents or necrosis.

INITIAL OBSERVATIONS FROM THE LITERATURE: LN IV-S VS IV-G

The distinction between LN class IV-S and IV-G has been the subject of three recent retrospective studies.[10–12] The three

studies, performed on different continents, have failed to show a worse outcome in LN IV-S vs IV-G, although there were some clinical and morphologic differences.[10–12] Mittal *et al.*[10] compared 11 patients who met criteria for LN IV-S with 22 patients with LN IV-G. Patients with LN IV-G had worse renal function and were more commonly hypertensive at baseline. With the exception of the distribution of lesions, both groups were similar with respect to other histologic parameters, activity and chronicity indices, treatment, and outcomes, leading the authors to conclude that the distinction between LN IV-S and IV-G 'may not be justified'.[10] Yokoyama *et al.*[11] evaluated a smaller, Japanese cohort that included 6 patients with LN IV-S and 17 with LN IV-G. The two groups were similar with respect to baseline clinical parameters. The mean renal survival was 95 months for LN IV-S vs 214 months for LN IV-G, although this difference did not reach statistical significance ($P = 0.1495$).[11] The findings in this study must be interpreted with caution because individual patients were not treated uniformly and patients with LN IV-S were less likely to have received aggressive therapy.

The largest study on LN IV-S and LN IV-G compared 15 French patients with LN IV-S and 31 with LN IV-G and found that at baseline, patients with LN IV-G had more proteinuria, renal insufficiency, anemia, and hypocomplementemia.[12] On pathologic evaluation, LN IV-G was associated with more membranoproliferative features, wire loop deposits and hyaline thrombi, greater IF positivity involving the peripheral capillary walls, and less fibrinoid necrosis. After initial biopsy, patients received steroids with or without cyclophosphamide and underwent a second protocol biopsy 6 months later. Clinical outcomes at 10 years follow-up were similar for patients with LN IV-S and LN IV-G diagnosed at the first renal biopsy. Over the initial 6-month interval, 30 of the 46 patients converted to mesangial proliferative LN (class II). Among the remaining 16 patients, the second biopsy showed transformation to IV-S in seven patients (all originally IV-G) and nine cases of IV-G (three of which were transformations from IV-S). Those patients with a 6-month biopsy diagnosis of LN IV-S had significantly better clinical outcome than those with IV-G.[12] The authors compared their findings to the previous two studies on LN IV-S vs IV-G[10–11] as well as the study by the Lupus Nephritis Collaborative Study Group[7] and concluded that while there are some clinical and pathologic differences between IV-S and IV-G, outcomes are similar.[12]

These studies have given us new insights into the IV-S/IV-G paradigm. Two studies have shown interconversion between IV-S and IV-G in repeat biopsies, arguing against the concept of distinct pathomechanisms of disease.[10,12] Thus the hypothesis that IV-S may represent an early stage in the evolution of class IV-G cannot be dismissed. Most of the studies have drawn analogies between 'pauci-immune' anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and LN IV-S, which often has prominent necrotizing features and minimal immune deposits.[7,10,12] Anti-neutrophil cytoplasmic autoantibody seropositivity is commonly encountered in patients with systemic lupus erythematosus[13] and cases have been described in which the disproportionate necrotizing and crescentic features in a patient with systemic lupus erythematosus led to the discovery of a positive anti-neutrophil cytoplasmic autoantibody, suggesting that overlaps between these disease processes can occur.[14,15] Despite these observations, no study has examined systematically the prevalence of anti-neutrophil cytoplasmic autoantibody seropositivity in cases of LN IV-S. Clearly, more studies addressing these differences are needed. Whether a distinction between IV-S and IV-G will be retained in future iterations of the classification should depend on whether it proves to have important clinical or pathogenetic implications.

INTEROBSERVER REPRODUCIBILITY

The success of a classification system is ultimately determined by its reproducibility and clinical relevance. A large study involving 20 centers in the UK recently found a significantly higher interobserver reproducibility for the ISN/RPS (2003) than the modified WHO (1982) classification.[8] In this study, renal pathologists classified cases of LN by the WHO system and then were asked to reclassify the same cases by the ISN/RPS 2003 classification 1 year later. The improved reproducibility of the ISN/RPS classification was ascribed to clearer separations between the classes and the elimination of subgroups of class V. The percentage of cases of class IV increased from 23% by the WHO 1982 classification to 46% by the ISN/RPS 2003 classification.[8] The increase in biopsy incidence of class IV could be attributed primarily to the elimination of class Vd as a subgroup of membranous and the inclusion of sclerotic glomeruli in the assessment of total glomeruli affected. The authors concluded that the ISN/RPS 2003 classification has achieved its goal of improved interobserver reproducibility, but warned that newer outcome studies based on the modern classification cannot be compared blindly to older studies employing earlier classifications without keeping in mind the differences in pathologic entry criteria. Another study has confirmed the higher consensus in reporting among pathologists using the 2003 ISN/RPS than the 1982 WHO classification.[11]

ISN/RPS CLASSIFICATION OF LN: STRENGTHS AND WEAKNESSES

What are the drawbacks of the new classification? There remains some confusion about the importance of subendothelial deposits in the diagnosis of class III and class IV. One of the most frequently asked questions is how to handle a case in which no subendothelial deposits or endocapillary lesions are visible by LM, but substantial subendothelial deposits are detected by IF or electron microscopy. In our view, such a case should be classified as class III if the subendothelial deposits involve $<50\%$ of glomeruli and class IV if they involve $\geqslant 50\%$ of glomeruli. A renal biopsy is always subject to sampling bias,

and it is important for the same pathologist to interpret and integrate the findings by all three modalities. This point may not have been adequately stressed in the original classification document. Implied by the ISN/RPS classification, but not explicitly stated, is that substantial subendothelial deposits are defining features of active class III and class IV, regardless of the proliferative pattern.

Another frequently asked question is how much active and chronic lesions are needed for the designations of 'A' and 'C'. According to the definitions proposed, a single glomerular lesion with any feature of activity is enough to assign 'A' for active. Similarly, a single segmentally or globally sclerotic glomerulus judged to be sclerotic as a consequence of scarred glomerulonephritis merits a designation of 'C'. Obviously the presence of high activity (vs low activity) is an important issue when deciding whether to pursue aggressive therapy, and there is no substitute for quantifying active and chronic lesions in the body of the microscopic description and on the diagnostic line.

Is the ISN/RPS classification of LN more clinically relevant than its predecessors? There is no doubt that elimination of the normal renal biopsy and the class Va-Vd subclasses are improvements. The use of (A) and (C) designations for active and chronic lesions has simplified reporting and given us a universal language that is easy to remember whether we are pathologists or clinicians. Clear definitions have allowed complex issues, such as the distinction between class IV-S and IV-G, to be rigorously tested at centers throughout the world.[10–12] Early indications that the ISN/RPS classification is more reproducible among pathologists must be considered a major achievement.

CONCLUSION

The ISN/RPS classification of LN represents a significant advance over the 1982 WHO schema. It is logical, easy to use, and highly reproducible. It has eliminated clinically irrelevant and cumbersome subclasses. The ultimate measure of acceptance of a new system is whether it is being used. A recent informal poll of an international group of renal pathologists at the International Academy of Pathology held in Montreal in September 2006 indicated by a show of hands that the vast majority of renal pathologists are using the new classification in their daily practice and consider it an improvement. Whether they follow the practice guidelines strictly is another issue, and admittedly some individual preferences prevail. The great strengths of the classification are that it has not made any major departures from accepted doctrines and that it is flexible enough to allow for future modifications as newer clinical and pathogenetic insights emerge. In the meantime it provides a valuable framework for well-defined prospective studies on treatment and prognosis. To what extent pathologic differences between the classes reflect pathogenetic differences is a much more difficult question that should pose the greater challenge for investigators in the years to come.[16]

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