Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices

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We present a consensus report pertaining to the improved clarity of definitions and classification of glomerular lesions in lupus nephritis that derived from a meeting of 18 members of an international nephropathology working group in Leiden, Netherlands, in 2016. Here we report detailed recommendations on issues for which we can propose adjustments based on existing evidence and current consensus opinion (phase 1). New definitions are provided for mesangial hypercellularity and for cellular, fibrocellular, and fibrous crescents. The term "endocapillary proliferation" is eliminated and the definition of endocapillary hypercellularity considered in some detail. We also eliminate the class IV-S and IV-G subdivisions of class IV lupus nephritis. The active and chronic designations for class III/IV lesions are replaced by a proposal for activity and chronicity indices that should be applied to all classes. In the activity index, we include fibrinoid necrosis as a specific descriptor. We also make recommendations on issues for which there are limited data at present and that can best be addressed in future studies (phase 2). We propose to proceed to these investigations, with clinicopathologic studies and tests of interobserver reproducibility to evaluate the applications of the proposed definitions and to classify lupus nephritis lesions.

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On May 9–11, 2016, a working group for lupus nephritis classification met at Leiden University Medical Center (Leiden, Netherlands) to reach a consensus on recently raised issues concerning problems with definitions of lupus nephritis lesions.[1] Prior to the meeting, those attending received a questionnaire asking for anonymous suggestions for improving the definitions. The responses served as a starting point for making adjustments to the definitions of lupus nephritis lesions, a process that was further accomplished by group discussions and a multi-head microscopy session. The group decided that consensus had to be reached for any proposed changes and that recommendations should be divided into 2 types. Phase 1 recommendations are clarifying modifications for which we could propose adjustments based on existing published evidence and mutual agreement. Phase 2 recommendations will address issues that can best be validated or modified through an evidence-based process. These include more problematic lesion definitions and adjustments to the lupus nephritis classification. We now report on phase 1 recommendations, and provide a framework for phase 2 issues.

Our immediate aim is to improve problematic definitions that form the basis of the lupus nephritis classification and thereby increase the interobserver agreement between nephropathologists worldwide who apply these definitions to classify lupus nephritis. Our eventual goal is to improve the lupus nephritis classification using an evidence-based approach, but refining the definitions for lesions is necessary because they form the essential elements for the classification. Here we describe a plan to proceed in the near future to gather data and, as indicated, modify the lupus nephritis classification.

Many renal lesions encountered in lupus nephritis also are present in other renal diseases, providing a rationale for harmonizing definitions for lesions irrespective of the disease context. Depending on the setting—that is, evaluation of renal biopsies in a clinical setting or for research purposes—different guidelines may apply regarding biopsy requirements. In a clinical setting, it is necessary to obtain as much information as possible from the biopsy by evaluating all stains in all levels and sections and to apply a basic format of the kidney biopsy report. As a general rule, 10 seems to be the appropriate number of glomeruli for evaluation. By studying definitions of frequently occurring lesions as currently formulated (e.g., as in classification systems for IgA nephropathy[2–4] and anti-neutrophil cytoplasmic antibody [ANCA]–associated glomerulonephritis,[5] as well as definitions created by the Neptune,[6] CureGN[7] and Banff[8] workgroups), we strove for uniform definitions but recognized that certain thresholds may be different among diseases. For example, it remains to be determined (an evidence-based phase 2 issue) which thresholds—for instance for mesangial hypercellularity—have clinical and prognostic value in lupus nephritis, and whether these should be different from those for another disease such as IgA nephropathy. Below, we discuss our modifications of definitions by class. Glomerular, tubulointerstitial, and vascular lesions are discussed separately. At this stage, we mainly focus on lesions evaluable by light microscopy, although we take into account findings by immunofluorescence (IF) and electron microscopy (EM) if they are helpful in the decision-making process. An overview of the alterations to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) lesion definitions and classification[9] that we propose is found in Table 1 and Figure 1.

GLOMERULAR LESIONS, CLASSES I VI

Classes I and II

An important question was the threshold between class I and class II. We questioned whether the current cutoff for mesangial hypercellularity implies that hypercellularity in merely 1 mesangial area in 1 glomerulus in the entire biopsy would suffice. We agreed that mesangial hypercellularity in 1 area in 1 glomerulus seems rather low. The appropriate threshold will be investigated in phase 2. In the meantime, we propose increasing the threshold of mesangial hypercellularity from 3 cells or mesangial areas to 4 cells, not including the hilar region, in line with the Oxford classification of IgA nephropathy,[2–4] and specify that mesangial cell nuclei be fully surrounded by matrix. An evidence-based approach to define an appropriate threshold was determined to be necessary. Whether and to what extent mesangial matrix expansion should be incorporated in the definition along with this cell number cut-off level also needs to be investigated in an evidence-based approach. Of note, only peripheral mesangial areas should be assessed for cellularity, with central and perihilar areas excluded, as described for IgA nephropathy. Importantly, we discussed whether hypercellularity within the mesangial zone caused by monocytes and/or macrophages, lymphocytes, or neutrophils should be considered as mesangial hypercellularity or as endocapillary hypercellularity. This topic will be discussed in more detail below.

Classes III and IV

A substantial amount of discussion centered on class III and IV lesions. We agreed, as previously noted, that the definitions of endocapillary "proliferation" are unclear and inconsistent,[1] with issues raised about the types and numbers of cells involved in endocapillary lesions, the definition of lumen reduction, and the specific contribution of endothelial cells. The group decided that the term ''endocapillary proliferation" is a misnomer that should be abandoned and replaced by the term "endocapillary hypercellularity," because most of the hypercellularity in glomerular capillaries in lupus nephritis is caused by influx of inflammatory cells rather than by actual cell proliferation. Phase 2 will address whether there should be, for instance, an overall glomerular inflammation score.

Endocapillary hypercellularity. Hypercellularity in lupus nephritis may be due to increase in cells in mesangial, endocapillary, and/or extracapillary locations. With regard to mesangial hypercellularity, it could be argued that this should be named mesangial hyperplasia in lesions purely consisting of an abundance of mesangial cells (Figure 2), representing lupus nephritis class II lesions. It is unknown whether the presence of inflammatory cells in the mesangium indicates a more active lesion; the cut-off values for mesangial hypercellularity and significance of mesangial inflammation remain to be determined in phase 2. Likewise, the cut-off levels for number of inflammatory cells, extent of capillary luminal narrowing and role of endothelial cell swelling need to be defined in phase 2. Figure 2 shows ultrastructural features of a single glomerular capillary affected by lupus glomerulonephritis. Inflammatory cells can be in the capillary lumen, beneath endothelial cells in capillary walls, and in the mesangial extracellular compartment. It has to be decided in phase 2 whether endocapillary hypercellularity should encompass all glomerular hypercellularity internal to the capillary wall glomerular basement membrane (GBM) and paramesangial GBM (excluding pure mesangial hyperplasia), or whether it should be restricted to an increase of cells within capillary lumens. Endothelial cell swelling alone was considered insufficient for a lesion to be regarded as representing endocapillary hypercellularity. If endothelial cell

Table 1 | Phase 1 recommendations for lupus nephritis classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class II	Definition for mesangial hypercellularity adjusted: Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region (A)	Cuttoff for mesangial hypercellularity unclear
Class III and IV	The term endocapillary proliferation is replaced by endocapillary hypercellularity (B)	Definition for endocapillary proliferation unclear; the term proliferation was considered imprecise
	The term crescent is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule should be involved.	Extracapillary proliferation involving > 25% of the circumference of Bowman's capsule was original cutoff. There were no definitions for fibrous or fibrocellular crescents
	Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix (C)	
	Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin (D)	
	Fibrocellular crescent: 25%–75% cells and fibrin and the remainder fibrous matrix (E)	
	Adhesion: an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis (F)	There was no definition for an adhesion
	Fibrinoid necrosis: fibrin associated with glomerular basement membrane disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis	There was no definition for fibrinoid necrosis
	Elimination of segmental and global subdivions of class IV	Definitions for segmental and global were unclear; interobserver variability was large; clinical significance uncertain
	Modification of the NIH lupus nephritis activity and chronicity scoring system (Table 2) to be used instead of the currently used A, C, and A/C parameters	Designation of activity/chronicity through A, C, and A/C considered too broad and nonspecific; preference for a semiquantitative approach to describe active and chronic lesions
Tubulointerstitial lesions	Indicate whether interstitial inflammation occurs in presence or absence of interstitial fibrosis	Lack of cut-off values for reporting the severity of tubulointerstitial lesions

A–F refer to typical examples of glomerular lesions in Figure 1.

swelling is encountered in the absence of inflammatory cells, thrombotic microangiopathy (TMA) should be considered, taking into account the number and extent of swollen endothelial cells and whether this is accompanied by subendothelial expansion or thrombosis. Relevant thresholds for this situation should be defined more precisely in phase 2. Hypercellularity external to the GBM is extracapillary hypercellularity.

Membranoproliferative glomerulonephritis (MPGN) pattern. We discussed the value of using the term "MPGN pattern" in relation to the modifications of definitions for lesions within class III and IV lupus nephritis. The group concluded that an MPGN pattern of injury is subsumed in class III and IV lupus nephritis as a form of endocapillary injury. We agreed with the ISN/RPS approach of considering subendothelial deposits that can be seen by light microscopy (i.e., wire loops) and hyaline masses within capillary lumens caused by immune complexes (i.e., hyaline thrombi) as lesions indicative of class III or IV. Determination of the clinical significance of the MPGN pattern and whether acute and chronic variants should be distinguished is a phase 2 exercise.

Crescents. The term "crescent" is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Because some crescents may have predominantly epithelial proliferation, whereas others consist predominantly of monocytes and/or macrophages, the group chose the description of a "variable mixture of cells." Fibrin and fibrous matrix may also be present. The ISN/RPS criterion of a crescent involving 25% or more of the glomerular capsular circumference was discussed. It was decided that this threshold should be 10% or more in accord with evidence from the Oxford Classification of IgA nephropathy and standard approaches used in clinical reporting of renal biopsy lesions. Crescents should be composed of more than 2 cell layers in order to distinguish them from apposition of the single layers of hypertrophied visceral and parietal cells. We propose definitions for the distinction of cellular, fibrous, and fibrocellular crescents, which were lacking in the ISN/RPS

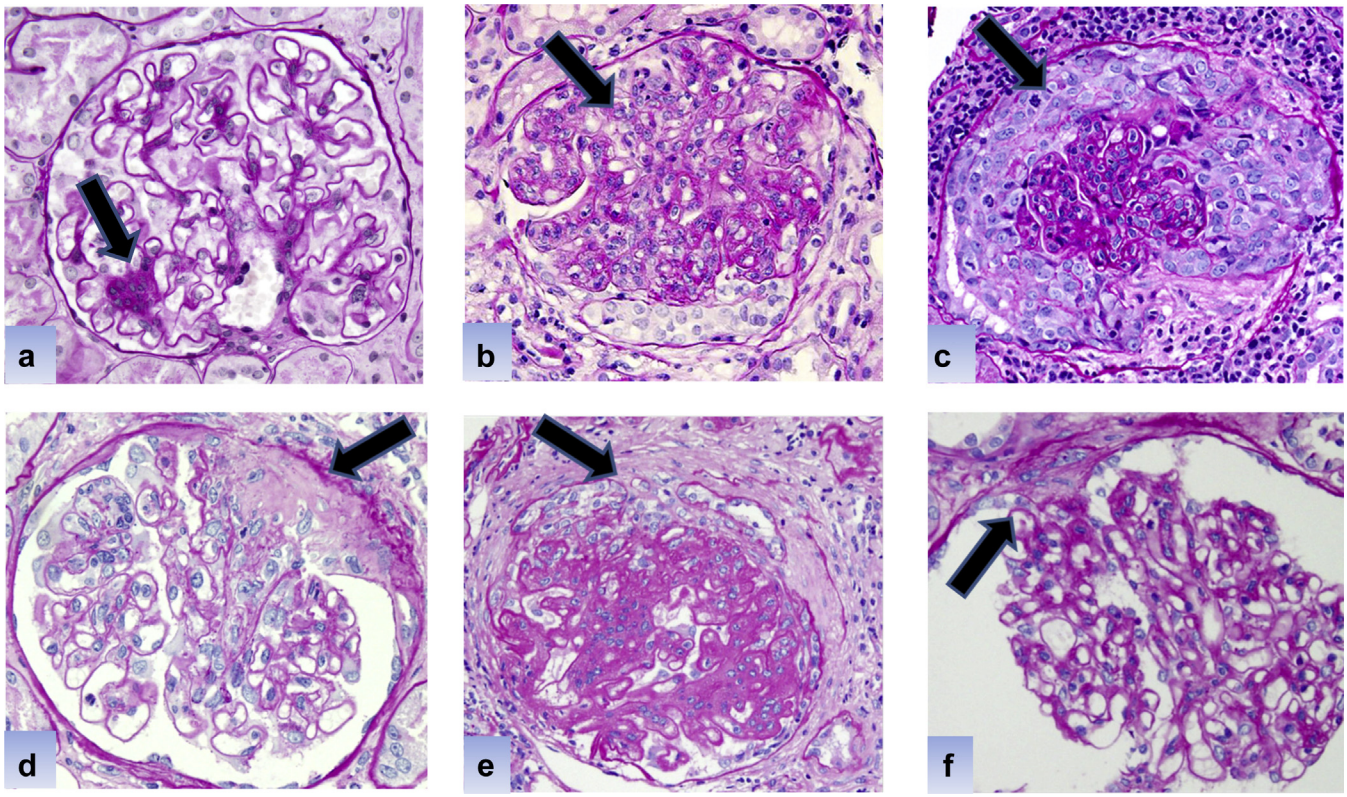

Figure 1 | Examples of glomerular lesions for which recommendations were made in Table 1. Arrows point to typical examples. All sections are shown in the PAS staining. (**a**) Mesangial hypercellularity, (**b**) endocapillary hypercellularity, (**c**) cellular crescent, (**d**) fibrous crescent, (**e**) fibrocellular crescent, (**f**) adhesion. PAS, periodic acid–Schiff. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

lupus nephritis classification (Table 1). Some glomeruli may have more than 1 type of crescent. In line with conventional nephropathology practice, extracapillary hypercellularity attributable to concurrent collapsing glomerulopathy lesions should not be designated as crescents. We propose to preserve the term "adhesion" for a lesion characterized by an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis. This is a lesion that is distinct from both crescents and segmental sclerosis, although this differs from the Oxford classification of IgA nephropathy in which such lesions are considered manifestations of segmental sclerosis. How to deal with a lesion characterized by cellular continuity between the tuft and Bowman's capsule that is not extensive enough to be called a crescent needs to be further discussed based on evidence acquired in phase 2.

Global/segmental. We previously discussed problematic issues concerning the distinction between segmental and global lesions in classes III and IV.[10] As recently demonstrated in a meta-analysis by Haring *et al.*,[11] the clinical importance of distinguishing between segmental and global lesions in class IV as defined by the ISN/RPS classification system has been questioned. A caveat is that there is poor interobserver agreement among nephropathologists worldwide in determining whether a glomerular lesion in lupus nephritis is segmental or global.[10] The latter, in combination with the uncertainty of how to evaluate the combination of intra- and extracapillary lesions into a segmental and/or global division, may have added greatly to the variability in outcomes of studies addressing the clinical impact of segmental and global lesions. The ISN/RPS approach to subclassifying class IV did not use segmental necrosis as a defining feature of a segmental variant of lupus nephritis, which may have reduced reproducibility and precluded recognition of a pathophysiologically distinct variant of lupus nephritis. Therefore, for phase 1, based on the lack of reproducibility and weak evidence of clinical significance, we propose to eliminate the S and G subdivisions of class IV. We believe that the distinction between segmental and global lesions should be retained in the microscopic description, as such distinctions still may prove to have clinical value with further study using the modified classification of lupus nephritis. As noted below, segmental fibrinoid necrosis as well as segmental endocapillary hypercellularity will be evaluated.

Fibrinoid necrosis. It was emphasized during the meeting that another potentially important feature not taken into consideration in the ISN/RPS identification of segmental lesions is the occurrence in lupus nephritis of fibrinoid necrosis. This is usually segmental and resembles lesions caused by ANCA-associated vasculitis. Conceptually, segmental endocapillary lesions may be merely a distribution variant of global endocapillary hypercellularity caused by the same

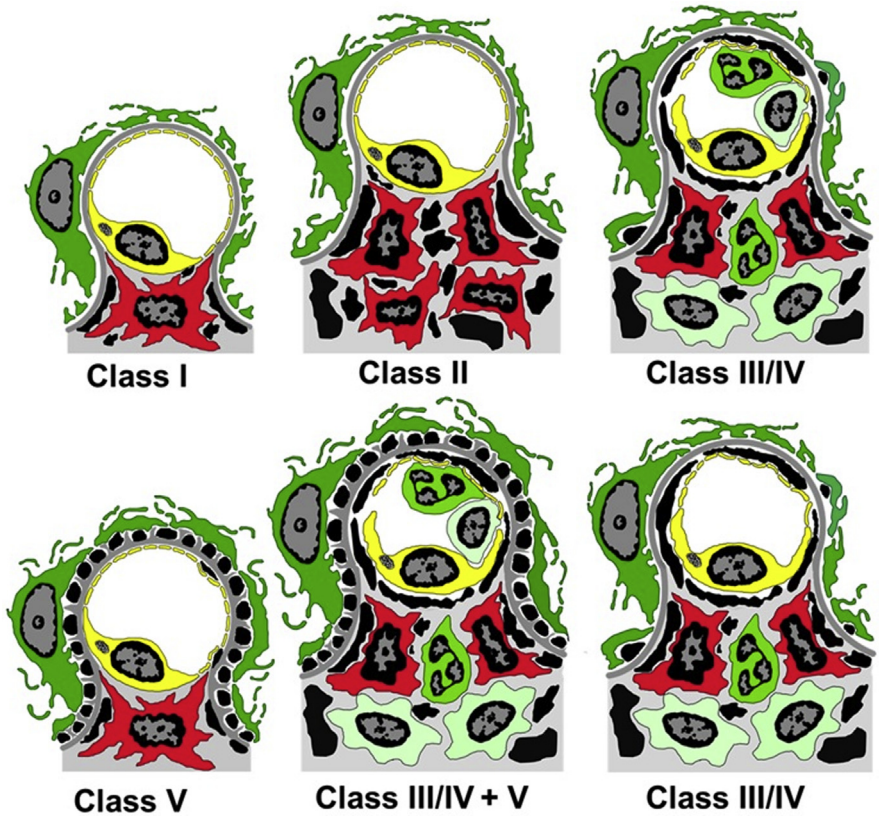

Figure 2 | Drawings depicting the ultrastructural features of a single glomerular capillary affected by lupus glomerulonephritis: class I with mesangial immune deposits (black) but no mesangial cell (red) hypercellularity or influx of leukocytes; class II with mesangial immune deposits and mesangial cell hypercellularity but no influx of leukocytes; class III/IV (upper right) with mesangial and capillary influx of leukocytes; class III/IV (lower right) with subendothelial capillary wall immune deposits that can be seen by LM and mesangial but no capillary influx of leukocytes (dark green neutrophils and light green monocytes/macrophages); class III/IV + V with an influx of leukocytes and numerous subepithelial immune deposits in addition to subendothelial deposits; and class V with numerous subepithelial immune deposits but no influx of leukocytes (podocyte = outer green cell, endothelial cell = yellow cell, mesangial cell = red cell, neutrophil = green cell with segmented nucleus, monocyte/macrophage = light green cell). LM, light microscopy.

pathogenic mechanisms, whereas segmental fibrinoid necrosis may be a pathogenetically distinct lesion. Therefore, for classes III and IV, we recommend noting the presence of fibrinoid necrosis. In phase 1, we propose to adjust the definition for fibrinoid necrosis in lupus nephritis as follows: fibrin associated with GBM disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis. Furthermore, karyorrhexis is defined as the presence of apoptotic, pyknotic and fragmented nuclei—a definition used uniformly in other classification systems. In phase 2, we propose that the clinical significance of fibrinoid necrosis should be reevaluated in addition to assessing the coexistence of necrotizing lesions with crescents. Whether these lesions have "pauci-immune" features by IF and/or coexistent ANCA serology[12] requires further study. The group concluded that phase 2 studies should determine and compare the clinical and pathogenic significance of karyorrhexis alone, which is common in class III and IV lupus nephritis, versus fibrinoid necrosis, which is less common.

Activity and chronicity assessment. For a critical re-evaluation of activity and chronicity, we turned to the paper by Austin *et al.*[13] on which the currently widely used National Institutes of Health (NIH) activity and chronicity index in lupus nephritis was based. This system can be used to report the extent of overall activity and chronicity in a semiquantitative way. It should be emphasized that this system has a number of limitations: the cut-offs for the scores 0 to 3 are arbitrary, and the scoring system was not developed using an evidence-based approach. Therefore, in phase 2, we will use an evidence-based approach without prior assumptions to modify these indices. We propose in phase 2 that the evaluation for active and chronic lesions in lupus nephritis should be refined to improve interobserver reproducibility and to validate prognostic value. In the meantime, we advocate the usage of these indices, but modified as indicated below, for all classes in a modified classification for lupus nephritis, thereby not restricting them to classes III and IV (Table 2). The modified NIH activity and chronicity scoring system provides more information than the shorthand A, C, and A/C parameters currently used. We decided it is important to retain total scores of 24 in the activity index and 12 in the chronicity index, in particular for comparing the scores recorded for earlier renal biopsy samples from the same patient using the original NIH scoring system. We therefore

Table 2 | Proposed modified NIH lupus nephritis activity and chronicity scoring system

Modified NIH activity index	Definition	Score
Endocapillary hypercellularity	Endocapillary hypercellularity in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Neutrophils/karyorrhexis	Neutrophils and/or karyorrhexis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Fibrinoid necrosis	Fibrinoid necrosis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	(0–3) × 2
Hyaline deposits	Wire loop lesions and/or hyaline thrombi in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Cellular/fibrocellular crescents	Cellular and/or fibrocellular crescents in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	(0–3) × 2
Interstitial Inflammation	Interstitial leukocytes in <25% (1+), 25%–50% (2+), or >50% (3+) in the cortex	0–3
Total		***0–24***
Modified NIH chronicity index	**Definition**	**Score**
Total glomerulosclerosis score	Global and/or segmental sclerosis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Fibrous crescents	Fibrous crescents in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Tubular atrophy	Tubular atrophy in <25% (1+), 25%–50% (2+), or >50% (3+) of the cortical tubules	0–3
Interstitial fibrosis	Interstitial fibrosis in <25% (1+), 25%–50% (2+), or >50% (3+) in the cortex	0–3
Total		***0–12***

NIH, National Institutes of Health.

continue to accord double weight to the presence of fibrinoid necrosis and cellular and/or fibrocellular crescents; results from our phase 2 study will be used to determine whether this approach is valid.

In the modified NIH activity index, we have made the following modifications: because in the original description of the combined karyorrhexis and fibrinoid necrosis category, the emphasis was on the presence of fibrinoid necrosis,[13] we have now modified this into a stand-alone category of fibrinoid necrosis, whereas we link the presence of karyorrhexis to neutrophil infiltration. Because most karyorrhexis represents apoptotic cell death of neutrophils, and because the original description for "leukocyte infiltration" refers to the presence of neutrophils only, we have changed the name and description of this category to indicate the presence of neutrophils and/or karyorrhexis. In the original description of the category "cellular crescents," it was unclear to what extent fibrocellular crescents should be included. Whereas fibrous crescents are part of the chronicity index, we have now included fibrocellular crescents in the activity index (see our proposal for definitions in Table 1). We refer to our considerations about the definition of endocapillary hypercellularity above: in the original description of Austin *et al.*,[13] only monocytes were taken into account in this category with respect to inflammatory cells leading to hypercellularity. We have to investigate in phase 2 how to approach the presence of inflammatory cells in endocapillary hypercellularity in more detail. For the moment, we find it important to specifically score neutrophils as a separate entity. In addition, the composition of the interstitial infiltrate as well as its presence in areas affected by interstitial fibrosis and tubular atrophy should be studied in further detail in phase 2.

Global and segmental glomerulosclerosis. We previously mentioned difficulties in the attribution of global glomerulosclerosis to either lupus nephritis or another cause,[1] an issue related to the classification of lesions into classes III and IV, which requires deciding whether global sclerosis is the sequel of an active class III and/or IV lesion. It was discussed that some globally sclerotic glomeruli show features that indicate lupus nephritis was the cause of the global sclerosis (e.g., fragmented tuft with surrounding fibrosis and extensive disruption of Bowman's capsule). Moreover, residual deposits other than IgM and C3 found by IF in globally sclerotic glomeruli should also be considered evidence that the lesion is the result of lupus nephritis. Globally sclerotic glomeruli should not be considered in the evaluation of lupus chronicity if they have a typical pattern of arterionephrosclerosis (e.g., subcapsular clusters of glomeruli with ischemic tuft collapse surrounded by collagen in Bowman's space). Incorporating globally sclerotic glomeruli that resulted from non-lupus injury in a chronicity index would overestimate the lupus nephritis chronicity and severity, but may still correlate with outcome. This issue should be addressed by phase 2 studies. It should be emphasized that in lupus nephritis the term "global sclerosis" is used for those glomeruli that are completely sclerotic, and that any other form of glomerulosclerosis should be regarded as segmental sclerosis. As mentioned previously, it is difficult to reliably differentiate segmental sclerosis as a consequence of class III and IV lupus nephritis from segmental sclerosis due to other causes (e.g., post-adaptive segmental sclerosis). Still, only the former should be designated as lesions of classes III and IV, employing the same features noted above to differentiate segmental sclerosis due to prior active lupus nephritis from that due to other causes. Within the chronicity index, segmental and global glomerulosclerosis are considered together.

Class V

Two issues were addressed in class V. First, we considered whether to distinguish class V with and without mesangial hypercellularity and agreed this decision should be evidence-based (phase 2). Second, phase 2 studies should determine the allowable extent of non–wire-loop subendothelial deposits within class V, above which one would have to classify as III + V.

Class VI

We recognize that the RPS/ISN category VI is rarely seen in renal biopsy specimens, and propose that this class be re-evaluated in phase 2, especially in view of our discussion above on the recognizability of globally sclerotic glomeruli resulting from preceding lupus nephritis active lesions versus nonspecific global sclerosis associated with other factors (e.g., aging, hypertension, or healed TMA lesions). Class VI will either need to be eliminated or some fraction of globally sclerotic glomeruli designated as the cut-off between chronic class IV and class VI.

TUBULOINTERSTITIAL LESIONS

We previously indicated the lack of cut-off values in the ISN/RPS classification for reporting of severity of tubulointerstitial lesions.[1] This deficiency will be addressed by the development of a valid activity and chronicity index that scores the severity of tubulointerstitial injury. We propose that in phase 2 we gather data on interstitial fibrosis and tubular atrophy and interstitial infiltrates in a semi-quantitative fashion, rounding fibrosis to the nearest 10%, with minimal fibrosis stated as 5%. These values then can be translated into reproducible scoring categories (e.g., on a scale of 0 to 3+) based on cut-off values to be evaluated for prognostic significance as currently done for the Banff and Oxford classifications. We advocate at this time, as a phase 1 recommendation, to indicate in biopsy reports whether interstitial inflammation occurs in the presence or absence of interstitial fibrosis. At present, interstitial inflammation remains part of the activity index as proposed above, while interstitial fibrosis and tubular atrophy remain as separate entities within the chronicity index. It has to be determined in phase 2 whether interstitial fibrosis and tubular atrophy should be considered separately or combined into 1 parameter (as in the Oxford classification for IgA nephropathy) and whether making a distinction between interstitial inflammation in areas with or without interstitial fibrosis has clinical significance.

VASCULAR LESIONS

Currently, the ISN/RPS lupus classification does not evaluate vascular lesions. We believe it is important to have a standardized approach and terminology to distinguish ordinary arterial or arteriolar sclerosis from lupus-related lesions such as vasculopathy associated with immune complex deposition, vasculitis, and TMA. In phase 2, a grading system for vascular lesions could be used following the Banff classification and the definitions of the Cure GN group for evaluating hyalinosis. Definitions for TMA and vasculitis in lupus nephritis still must be created, as they can occur in an isolated manner with or without associated specific serologic findings (ANCA, APA, etc.) or coexist with immune complex–mediated lupus glomerular lesions. We propose that lupus vasculopathy be defined as luminal narrowing of arterioles or terminal interlobular arteries by intramural immune deposits, typically admixed with fibrinoid changes, without inflammation of the vessel wall. The Ig and complement composition of the deposits is confirmed by IF.[14–16] Future studies will determine any impact of such lesions on prognosis and response to treatment.

SUMMARY AND FUTURE DIRECTIONS

In our efforts to work toward a more effective, more reproducible, and more valuable classification for lupus nephritis, we have proposed improvements in the definitions of lupus nephritis lesions, which could impact treatment and prognosis. We have also proposed 2 important alterations in the classification system, namely to abandon the segmental and global designations in class IV, and to replace the A, C, and A/C designations of classes III and IV by use of modified NIH lupus nephritis activity and chronicity scoring indices. Our proposed modifications are based on published evidence, expert experience, and mutual agreement; we regard this as a phase 1 venture. The new definitions for lesions in lupus nephritis and the modifications to the classification system address some of the disagreement that currently exists among nephropathologists worldwide in classifying lupus nephritis according to the ISN/RPS lupus nephritis classification.

We would like to emphasize that many of the proposed changes involve descriptions of lesions that in other settings, such as the Oxford classification of IgA nephropathy, have proven challenging even for experienced pathologists to reliably reproduce. We will proceed to a phase 2 evidence-based approach using clinicopathologic studies and tests of inter-observer reproducibility to evaluate and validate the value of the newly proposed definitions and adjustments to the classification system and include tubulointerstitial and vascular lesions. This will entail a process similar to that used to develop the Oxford classification for IgA nephropathy—that is, scoring of individual lesions by multiple pathologists in lupus nephritis biopsies obtained from patients for whom clinical outcomes are available. Once these data become available, it will be possible to modify the currently used cut-off points to optimize the classes of lupus nephritis and to develop and validate reproducible activity and chronicity indices that are of clinical utility.

DISCLOSURE

All the authors declared no competing interests.

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