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