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Systemic lupus erythematosus: pathogenesis, diagnosis, and treatment

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The Revisited Classification of Glomerulonephritis in Systemic Lupus Erythematosus at 10 years: Time to Re-evaluate Histopathologic Lesions

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Abstract

Over 10 years have passed since the latest revision of the histopathologic classification of lupus nephritis. This revision was a significant improvement compared to the previous version, mainly because of clearer and more concise definitions and the elimination of mixed subclasses. Despite these improvements, there are still some difficulties in the classification for lupus nephritis, many of which are in the definitions provided. In this review, we focus on the difficulties surrounding the evaluation of classes III and IV lesions, particularly the definitions of endocapillary and extracapillary proliferation, the use of the terms endocapillary proliferation and hypercellularity, the clinical relevance of segmental and global subdivisions in class IV, and the value of distinguishing lesions that indicate activity and chronicity. Vascular and tubulointerstitial lesions are also discussed. Furthermore, we give an overview of the history of the classification to provide background on the origin and development of the definitions in lupus nephritis. The issues raised in this review, as well as the suggestions for improvements may assist with a revision of the lupus nephritis classification in the near future.

Introduction

Over 10 years have elapsed since the latest revision of the classification of glomerulonephritis (GN) in SLE, which also known as the International Society of Nephrology/ Renal Pathology Society (ISN/RPS) lupus nephritis (LN) classification.^{1,2} This revision is generally considered an improvement to the previous classification. The improvement was mainly attributed to clearer and more precise definitions of classes and lesions and elimination of the mixed subclasses of membranous LN and class III/IV lesions, which led to a relatively high reproducibility compared with previous versions.^{3,4} Nevertheless, from experience in a group of nephropathologists who specialized in LN, it became apparent that there are still many difficulties in the current version of the classification, mostly originating from uncertainties and inconsistencies in the definitions of histologic parameters. In a recent study focussing on class III and IV lesions, considerable interobserver variation among nephropathologists in evaluating these lesions was shown.⁵ Taking the opportunity to further improve the classification may add to its usefulness in clinical practice and to better interobserver agreement among nephropathologists. Therefore, the purpose of this paper is to provide a critical reading of the latest version of the classification,^{1,2} list points to be considered for clarification, and offer suggestions for improvements, which may be used to guide a revision of the classification in the near future.

Biopsy requirements

Reporting of the number of glomeruli in a biopsy confers a level of certainty with regard to the accuracy of the assigned class.⁶ In the ISN/RPS classification paper,^{1,2} a minimum of 10 glomeruli is advised for the classification of LN, but it is uncertain what to do with incomplete glomeruli on the edge of the biopsy or small tangential sections of glomeruli. For research purposes, such as in the Oxford IgA nephropathy (IgAN) classification,⁷ a glomerulus is required to have at least three mesangial areas to be included in the number of glomeruli scorable for mesangial hypercellularity.

In the ISN/RPS classification paper^{1,2} it is recommended to cut the biopsy at multiple levels. Although useful in clinical practice, it is a complicating factor in classifying LN, because there are no guidelines on how to establish the final decision on class after this exercise. It is cumbersome and not always possible to track each glomerulus through different levels. Furthermore, it is currently unclear if a glomerular lesion should be designated as segmental or global when this differs between multiple levels of the same glomerulus. The segmental or global involvement of a glomerulus already has been shown to have low interobserver

agreement when one the basis of one glomerulus at one level.⁵ All of these considerations are of particular importance in LN, because they can make the difference between class III and IV or between classes IV-segmental (IV-S) and IV-global (IV-G), the latter distinction being especially complex and controversial. We conclude that more specific guidelines are needed on how to deal with multiple levels and incomplete glomeruli in classifying LN.

Classes I and II

The lack of quantitative guidelines, which ideally would define cutoff values, is a common problem in many definitions, despite the improvements already made in the ISN/RPS classification. In class I, glomeruli show deposits by immunofluorescence and electron microscopy, whereas they should appear normal by light microscopy. Class II is defined as mesangial proliferative LN. This class is characterized by any degree of mesangial hypercellularity, where the hypercellularity is defined as three or more mesangial cells per mesangial area in a 3-micron-thick section. The origin of this cutoff is unclear. The only previously described cutoff stems from the 1974/1975 World Health Organization (WHO) classification,⁸ in which mesangial hypercellularity is defined as more than three cells per mesangial area away from the vascular pole (Box 1). The latter is equivalent to the Oxford IgAN classification, where mesangial hypercellularity is defined as four or more mesangial cells per area⁷ rather than three or more cells. In LN, although three or more cells in a mesangial area is a clear-cut guideline, there is, unfortunately, limited information on the extent of mesangial proliferative lesions necessary to classify a biopsy as class II. The definition that any degree of mesangial proliferation would suffice for class II implies that one glomerulus, independent of the total number of glomeruli, with one mesangial area containing three cells would be enough to classify the biopsy as class II. It is questionable if this is what was meant. Ultimately, it may be questioned if the amount of mesangial proliferation defining either class I or II has any clinical relevance. This was at least not what was intended in the current division in class I and II. Apart from mesangial cell proliferation, mesangial matrix expansion is also used to define class II (table 3 in the ISN/RPS classification paper¹²). However, no definition of mesangial matrix expansion is given.

It is not entirely clear how many subepithelial and subendothelial deposits are allowed in class II. It is stated that “a few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy”.¹² Quantifying what is meant by a few isolated subepithelial or subendothelial deposits would be helpful to make the diagnosis of class II LN more straightforward and most importantly, to clearly

Box 1: A history of lupus nephritis with a focus on terminology

1955

Preceding the first attempt towards a classification of LN in 1964, Pirani and Pollak in collaboration with Muehrcke, Kark, and Steck reported in detail on the individual histologic lesions in LN in 1955.³⁸ Muehrcke *et al.*³⁸ reported that the earliest detectable histologic lesions consisted of minute foci of hypercellularity at the periphery of the glomerular tufts as a result of endothelial cell proliferation. This was called local glomerulitis. Local was used, because initially, the lesion consisted of one or two patches of proliferating endothelial cells near the periphery of the tuft. The term proliferation in this article is always used in conjunction with the endothelium. It uniquely referred to endothelial proliferation, although this was never actually proven.

1964

The Natural History of Renal Manifestations of SLE was reported on in 1964³⁹ (a reprint of this article together with the original authors' comments appeared in 1997 in JASN⁴⁰). Histologic findings in 176 renal biopsy and necropsy specimens were grouped according to the following categories: (1) no histologic evidence of renal involvement, (2) lupus glomerulitis, (3) active lupus GN, and (4) membranous lupus GN.

Among the histologic findings considered to reflect the presence of activity was cellular proliferation in glomeruli. The description of lesions found in the four classes in the 1964 article³⁹ are at the basis of the classification of LN as we know it today. It is interesting that, in these early beginnings, confusion on how to define the separate components of the glomerular changes already became apparent. Lupus glomerulitis was distinguished from active lupus GN. Most likely, this distinction hinged on whether the interstitium was involved in the inflammation, but there were also glomerular lesions that were more characteristic of one versus the other. Local necrosis, obliteration, karyorrhexis, and fibrinoid changes are specifically mentioned as part of lupus glomerulitis. For active lupus GN, areas with glomerular hypercellularity and on occasion, the occurrence of a few polymorphonuclear leukocytes were mentioned.

1970

Baldwin *et al.*⁴¹ described clinical histopathologic correlates of patients with focal proliferative LN, diffuse proliferative LN, or membranous LN. It was observed that in focal LN, for the most part, only small portions of glomeruli were affected, whereas in diffuse LN, usually larger

portions of each glomerulus were involved. Cutoff points in terms of percentages were not given. The difference in morphologic appearance, severity, and clinical course was suggested to point towards different pathogenic mechanisms.

1974/1975

The WHO classification for LN resulted from deliberation at international conferences in Buffalo, New York and Geneva, Switzerland in 1974 and 1975, respectively. An official WHO classification was never published in the peer-reviewed literature; however, the first journal article that referred to the classification was by Appel *et al.*⁸ in 1978. This WHO system included a purely mesangial form of LN as well as focal, diffuse, and membranous forms. The pathologic definition of the purely mesangial form of LN was already quite complex: “segmental or global, focal or diffuse hypercellularity confined to the mesangium – more than three cells per mesangial area away from the vascular pole in two to four micron sections and/or increased matrix with widening of the mesangial stalk”.⁸ Zimmerman *et al.*⁴² had independently described the mesangial proliferative variant in 1975, and Baldwin *et al.*⁴³ added this variant to their classification in 1977.

In the publication by Appel *et al.*,⁸ 56 patients with LN were entered into a clinicopathologic analysis using the WHO classification from 1974/1975, and Roman numerals were, for the first time, used to identify the different classes. In this 1978 publication, descriptions of the five classes were enriched by immunofluorescence and electron microscopy data.⁸ In fact, in the discussion, Appel *et al.*⁸ concluded that the location of immune complex deposits as defined by immunofluorescence studies and the host response that these immune complexes stimulate form the basis of the histologic classification of LN. Although classes III and IV were regarded as two forms of LN reflecting different stages of the same process, it was also mentioned that class IV may have a membranoproliferative variant.

1982

Eight years after the introduction of the first WHO scheme, it was modified by a consensus conference held during the International Study of Kidney Diseases in Children Meeting in Paris in 1980.⁴⁴ Instead of the 50% cutoff to differentiate between classes III and IV, which was introduced in the 1974/1975 version, class III was defined as focal segmental GN, and class IV was defined as diffuse GN. Because of the lack of a definitive explanation of the distinction between classes III and IV, there was substantial controversy over the importance of segmental

inflammatory lesions versus % of glomeruli involved in distinguishing between classes III and IV. Classes III and IV were subdivided into three and four subclasses, respectively. Also, class V was subdivided for the possible combinations with class II, III, or IV LN. Finally, class VI (advanced sclerosing GN) was introduced but not specifically defined. This classification was considered too complicated by many pathologists, causing them to continue using the unofficial version published by Appel *et al.*⁸

1995

Additional modifications were made and published in the second edition of the book on the classification of glomerular diseases by Churg *et al.*⁴⁵ These modifications consisted of the elimination of classes Vc and Vd to describe combined membranous and class III or IV LN. Also, the original 50% cutoff in class III versus class IV was mentioned again, but it was stated that "... this division is not clear-cut. Rather there is a continuum of changes, and the clinical behavior usually parallels the proportion of involved glomeruli. It might be better, therefore, to include all cases of proliferative LN in class IV and to specify the degree of involvement as mild, moderate, or severe. The class III designation should be reserved for cases with focal segmental necrotizing lesions".⁴⁵

2004

Another classification was proposed by the ISN/RPS Consensus Conference on the Classification of Lupus Glomerulonephritis. This system resembled the WHO system but has more detailed definitions and clearer distinctions among the classes.¹² Notably, in the overview of the classes, classes III and IV are not called proliferative, because pure chronic sclerosing lesions were also included. This is in accord with the WHO classification, which also did not use proliferative in the diagnostic terms for class III and IV^{44,45}; however many published accounts of the classification inserted the term proliferative inappropriately, and the term has been widely used in practice. This probably stems from the use of proliferative in the unofficial reference to the WHO classification in the article by Appel *et al.*,⁸ which used terminology in use by Baldwin⁴¹ and Pirani.³⁹ In the current classification, the term proliferative is still used in the description of the classes III/IV-A(C).LN, for the most part, only small portions of glomeruli were affected, whereas in diffuse LN, usually larger portions of each glomerulus were involved. Cutoff points in terms of percentages were not given. The difference in morphologic appearance, severity, and clinical course was suggested to point towards different pathogenic mechanisms.

distinguish it from class III. However, it would be challenging to establish an evidence-based quantitative standard for this using information currently available.

Class III and IV

Endocapillary proliferation

Endocapillary proliferation, a key feature of active classes III and IV LN, is defined as: “endocapillary hypercellularity due to an increased number of mesangial cells, endothelial cells, and infiltrating monocytes, and causing narrowing of the glomerular capillary lumina” (table 5 in the ISN/RPS classification paper^{1,2}). The increased number of mesangial cells in this definition could be confusing, because it is stated in table 3 of the ISN/RPS classification paper^{1,2} that classes III and IV are characterized by GN with or without mesangial alterations. What is also not clear from the definition is whether all or only some of the mentioned criteria should be present. The wording suggests that all items should be present. In our experience, many nephropathologists would call lesions, such as those depicted in Figure 1, A and B, endocapillary proliferation, although some of the mentioned criteria are lacking. Of interest is the mention of the monocyte as the inflammatory cell characteristic of endocapillary proliferation (table 5 in the ISN/RPS classification paper^{1,2}), whereas in table 6 of the same paper,^{1,2} under the descriptions of active lesions, the looser term leukocyte infiltration is used. Substantial luminal reduction is also part of the definition, but how substantial remains unclear. These issues together have probably contributed to the high interobserver variation in recognizing these lesions, which was shown in a recent study.⁵ Another important source of interobserver variation in LN seems to lie in the confusion around the terms proliferation and hypercellularity. In *Dorland’s Illustrated Medical Dictionary*,⁹ proliferation is defined as “the reproduction or multiplication of similar forms ... see also hyperplasia and hypertrophy”, and hypercellularity is defined as “a state characterized by an abnormal increase in the number of cells present, ...”. It is likely that part of what we consider endocapillary proliferation in LN is not actually “reproduction or multiplication of similar forms”, although many instances do represent “a state characterized by an abnormal increase in the number of cells”.⁹ Often, we do not exactly know which cell types are responsible for what we call endocapillary proliferation or hypercellularity. In our opinion, the lesions characteristic of classes III and IV LN should be clearly redefined, because both there is the large interobserver variation with respect to these lesions⁵ and the same terminology is beginning to cause similar problems in other areas of nephropathology, such

as IgAN (I. Bajema, M. Haas, and T. Cook, personal communications). An option would be to avoid the term proliferation altogether, which would have the added benefit of avoiding confusion around the term mesangial proliferative LN for class II.

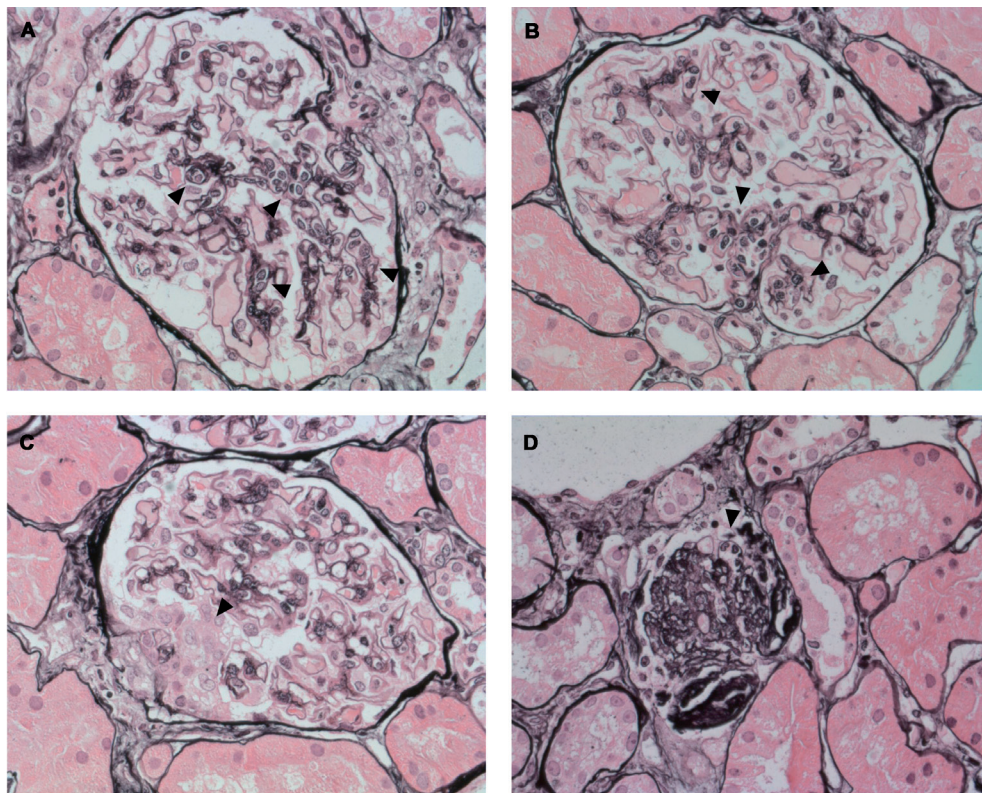


Figure 1. Examples of problematic lesions in LN

(A and B) Is this endocapillary proliferation according to the definition? Arrowheads point to areas that could signify endocapillary proliferation, because there is reduction of the capillary lumen most likely caused by influx of inflammatory cells and/or endothelial swelling. (C) Is this extracapillary proliferation (arrowhead)? According to the classification, it does not qualify, because it spans <25% of the capsular circumference. (D) A globally sclerosed glomerulus located not far from the capsule and adjacent to another globally sclerosed glomerulus (not shown). Is this global sclerosis caused by LN or to another cause? The arrowhead points to two inflammatory cells in the capillary lumen. Silver methenamine stain. Original magnification, X 400.

Extracapillary proliferation

The evaluation of extracapillary proliferation is another challenging issue in classes III and IV LN. The definition of extracapillary proliferation or a cellular crescent given in table 5

in the ISN/RPS classification paper^{1,2} is “extracapillary cell proliferation of more than two cell layers occupying one fourth or more of the glomerular capsular circumference”. This definition only holds for a cellular crescent; fibrocellular and fibrous crescents lack a definition. Fibrocellular and fibrous crescents are only mentioned in table 6 of the ISN/RPS classification paper,^{1,2} which states that both cellular and fibrocellular crescents are regarded as active lesions and that fibrous crescents are regarded as chronic lesions. The “one fourth or more of the glomerular capsular circumference” is an addendum that many nephropathologists probably disregard, because it would entail that a lesion, such as depicted in Figure 1C, would not be considered to represent extracapillary proliferation. How extracapillary proliferation contributes to determining whether a biopsy falls into either the IV-S or IV-G subcategories is a complicated issue. The segmental or global character of class IV lesions is defined by the extent of the lesions within the glomerular tuft, which consists of glomerular capillaries and mesangial cells,¹⁰ and does not include Bowman’s space and Bowman’s capsule. By definition, therefore, extracapillary proliferation can never contribute to the segmental or global nature of a class IV lesion. If we want to include extracapillary proliferation when assessing the segmental or global nature of the lesion, the area should be redefined in which both endocapillary and extracapillary lesions can occur to establish whether we are dealing with segmentally or globally affected glomeruli. Finally, the term extracapillary proliferation holds some of the same objections as the term endocapillary proliferation. Therefore, one could consider using the term extracapillary hypercellularity rather than extracapillary proliferation.

Segmental and global subdivision

There is a belief among many nephropathologists and nephrologists that a subclass of LN characterized by segmental lesions with fibrinoid necrosis resembling those typically seen in ANCA-associated vasculitis would be clinically relevant. In the latest version of the classification, the segmental and global subdivision within class IV was introduced. This subdivision was based on data from a study by Najafi *et al.*¹¹ suggesting that this would lead to a subclass of segmental lesions, which comprised the more vasculitic-like lesions in LN, possibly with poor outcome. In a recent meta-analysis by Haring *et al.*,¹² it was demonstrated that there is little clinical significance in relation to outcome of segmental and global LN, as defined in the ISN/RPS classification.^{1,2} However, before a final decision is made regarding potential elimination of the IV-S and IV-G subcategories, it should be considered how the definitions of segmental and global were applied in different studies. Most notably, Najafi *et al.*¹¹ defined their segmental lesions differently from the definition given in the ISN/RPS

classification,¹² including lesions involving >50% but not the entire glomerular tuft. In a later study of Schwartz *et al.*¹³ these latter lesions, which they termed class IV-Q, were found to have a worse prognosis than segmental lesions involving <50% of the tuft or lesions involving the entire tuft. An older study by Schwartz *et al.*¹⁴ from 1987 did not show a difference in prognosis between cases with segmental (subtotal) involvement of the tuft in more than 50% of glomeruli and patients with a diffuse pattern in >80% of glomeruli. We conclude that it is, thus far, unclear what subdivision (if any) within classes III and IV would be of clinical or prognostic relevance. Most importantly, the premise of the vasculitic-like lesion, which is at the basis of a possible subclass, in time was replaced by the notion of a segmental lesion. It seems evident that, whereas most vasculitic-like lesions will be segmental, many other segmental lesions exist that are not vasculitic-like. Because of the many different definitions that were used in different studies, it seems that only by starting from scratch with new data will it become possible to investigate this issue for future purposes.

Activity and chronicity

In table 6 in the ISN/RPS classification paper¹² a summary is given of markers of activity and chronicity of LN to be included in the report. Presumably, these also serve as guidelines towards the usage of the active (A), chronic (C), and A/C subclasses, which are important for making treatment decisions. Although this is incorporated in classes III and IV by the addition of A, C, or A/C, this denotation does not provide any information on the extent of the activity or chronicity. Therefore, it is recommended in the ISN/RPS classification paper¹² to report the proportion of glomeruli affected by active and chronic lesions in the diagnostic line. Also the proportion of glomeruli with fibrinoid necrosis and crescents should be reported. Furthermore, it is stated that the activity and chronicity indices by Austin *et al.*¹⁵ can be used. However, the added benefit of these indices is unclear. So far, they have not unequivocally been shown to be of prognostic value when added to clinical information and the histologic class.¹⁵⁻¹⁹ Moreover, they do not show good reproducibility.^{20 21} There are some lesions for which the A or C status is debatable (*e.g.*, the membranoproliferative pattern, of which it is stated that this pattern “...is particularly common in the chronic phase of lupus nephritis”;¹² although no literature reference is provided). Another issue is global glomerulosclerosis. If considered to be the consequence of LN, global sclerosis is cause to designate the biopsy as having a chronic component, but it can be very difficult and often impossible to determine whether global glomerulosclerosis is the result of LN or another cause (Figure 1D). This is also the case for other chronic glomerular lesions, particularly segmental sclerosis, which may result from podocyte injury (*e.g.*, in class V lesions as

discussed below) or postinflammatory scarring. Nevertheless, such lesions may lead to a classification of LN class III C or IV C, with the potential for clinical confusion. To make the distinction between nonspecific glomerulosclerosis and chronic lupus lesions, it may be helpful to look at the location of the glomerulus in question within the biopsy (subcapsular or not), other signs of ischemia, signs of previous active lesions (for example, a convincing fibrous/fibrocellular crescent), or a fragmented-appearing scarred tuft.

Class V

The definition of class V LN seems quite straightforward. The major difficulty is in chronic lesions. It is mentioned that, as class V evolves to chronicity, the development of segmental or global glomerulosclerosis is typical. However, if segmental or global glomerulosclerosis is regarded as sequelae of class III/IV lesions, the biopsy should be designated as class III/IV C + V. Similar to the discussion raised above, it may be challenging to reliably distinguish between segmental or global sclerosis caused by class III/IV or V LN. Review of previous biopsies, if available, for any active class III/IV lesions and subendothelial deposits may be helpful in making this distinction.

Class VI

The definition of class VI LN is relatively straightforward, being on the basis of >90% of globally sclerotic glomeruli without any active glomerular lesions. The primary reason for including this cutoff was to end the arbitrary use of class VI in the WHO system, with some pathologists using class VI for >50%, others >75% or 80% global sclerosis. However, >90% global sclerosis is a rare event, and one may ponder about its clinical usefulness. This class could be combined with biopsies otherwise classified as pure chronic class III or IV as a new chronic LN class VI, in which the extent of sclerosis has to be specified. This has practical implications, in that none of the pure chronic lesions are likely to benefit from immunosuppressive treatment, although the management of the individual patient may vary depending on the percentage of sclerosed glomeruli and clinical presentation.

Glomerular lesions not included in the classification

Apart from the typical histopathologic glomerular lesions on which the classification is based, a number of other glomerular lesions may be encountered. Although these lesions are not part of the classification, they do require the attention of the pathologist and should be reported in the diagnostic line. These lesions include (lupus) podocytopathy, collapsing

glomerulopathy, and thrombotic microangiopathy (TMA). The latter can occur within the context of antiphospholipid syndrome nephropathy, which has been shown to be present in 10%-32% of biopsies with LN.²²⁻²⁴ However, TMA is not specific for antiphospholipid syndrome nephropathy and can also be seen in, for example, malignant hypertension. In some patients with SLE and a nephrotic syndrome, diffuse foot process effacement without capillary wall deposits can be found by electron microscopy. This finding can be either coincidental idiopathic minimal change disease or more likely, some form of lupus podocytopathy, possibly mediated through T cell activation in SLE.²⁵⁻²⁷ Finally, collapsing glomerulopathy can sometimes be encountered in patients with SLE either with or without concomitant LN. Whether this represents coincidental idiopathic collapsing glomerulopathy or should be seen in the context of a lupus podocytopathy remains to be determined. An argument in favor of the latter is that, in the largest patient series reported, 16 of 19 patients had active extrarenal lupus symptoms at time of biopsy.²⁸

Vascular lesions

In the current classification, little attention is given to vascular lesions in lupus, although they do seem to have clinical significance. The most common lesion is the presence of isolated immune complex deposits. Furthermore, TMA, lupus vasculopathy, and arterioarteriolosclerosis can occur, while vasculitis is uncommon²⁹; Banfi *et al.*³⁰ showed decreased renal survival if one of the latter four lesions was present. Although it was thought that isolated vascular immune complex deposits did not affect outcome, in a recent study by Wu *et al.*,³¹ a worse renal outcome was shown. The current classification does recommend reporting vascular lesions, such as vascular deposits, thrombi, vasculitis, or sclerosis, in the diagnostic line and grading them as mild, moderate, or severe. Specific criteria for this grading are not provided. For intimal sclerosis, it can be considered to use the cutoff values set in the Banff classification of renal transplant biopsies.³² It has been suggested that the inclusion of a detailed description of renal vascular lesions in the ISN/RPS classification of LN may strengthen the predictive value for renal outcome.³¹

Tubulointerstitial lesions

Tubulointerstitial lesions are correlated with glomerular lesions, but they have also been shown to be prognostic of renal outcome in LN independent of glomerular lesions.³³ Therefore, tubular atrophy, interstitial inflammation, and fibrosis have to be reported in the diagnostic line and graded as mild, moderate, or severe. No cutoff values for this grading

system are provided. It is also unclear if all three parameters should be graded separately or can be combined into one grade for tubulointerstitial damage, because interstitial fibrosis and tubular atrophy have been shown to correlate with tubulointerstitial inflammation in LN.³⁴ Interestingly, the possible significance of tubulitis in LN has not yet been studied extensively. The reported interobserver agreement for visual assessment of tubular atrophy and interstitial fibrosis using routine stains applied in nephropathology is quite variable.^{7 35} ³⁶ The reproducible approach reported in the Oxford IgAN classification,³⁷ in which tubular atrophy and interstitial fibrosis are combined into one grading system, therefore seems most practical.

Concluding remarks

We have given a close reading of the latest version of the LN classification, pointing out problematic issues in the definitions of histopathologic lesions used to classify LN. Solving these problematic issues is not an easy task. Importantly, one has to realize that, in making workable definitions, there is a delicate balance between maximum precision and Gestalt interpretation. Strict definitions may be most useful for research studies and relatively inexperienced nephropathologists, whereas Gestalt interpretation may sometimes serve clinical practice better, because it allows for a more liberal interpretation by experienced pathologists, which may sometimes overrule the strict boundaries of the definitions. The latest version of the classification reflects the compromises that have been made in the very long history of this classification, in which many experts over the years have tried to capture the complex nature of LN. For details on the historic development of the terminology, we refer to Box 1. The lupus classification is one of the few nephropathologic classifications that is closely linked to therapeutic interventions, making it clinically very relevant. Therefore, it is of the utmost importance to clearly define the histopathologic lesions, which form the basis of the classification, to obtain good interobserver agreement among nephropathologists worldwide. In addition, future iterations of the classification may incorporate certain immunologic and/or molecular markers if they are shown to improve diagnostic accuracy and/or clinical correlation beyond histology alone. Points of consideration for further improvement of the classification are listed in Table 1.

Disclosures

None.

Table 1. Concerns and suggestions for improvement for the future revision of the LN classification

Topic and Concerns	Suggestions for Improvement
<p>Biopsy requirements</p> <p>No details on how to deal with small or incomplete glomeruli</p> <p>No guidelines on how to establish the final decision on classification after evaluation of multiple levels</p>	<p>Following the Oxford IgAN classification: include glomeruli with at least three mesangial fields in the number of scorable glomeruli</p> <p>No clear-cut suggestions from the literature; needs to be further discussed</p>
<p>Class II</p> <p>Mesangial proliferation</p> <p>It is unclear if the current cutoff for mesangial hypercellularity (three mesangial cells per mesangial area) implies that hypercellularity in one mesangial area suffices for a diagnosis of class II</p> <p>Any degree of mesangial matrix expansion (not further defined) is mentioned to be part of mesangial proliferative LN (class II), but it is unclear if and how this is part of the definition</p> <p>Subendothelial or subepithelial immune complexes</p> <p>By EM or IF, scattered immune complexes are not defined</p>	<p>Redefine cutoff; consider guidelines as used in the Oxford IgAN classification for mesangial hypercellularity and mesangial matrix expansion</p> <p>Alternatively, an evidence-based approach in LN specifically can be considered</p> <p>Define what scattered immune complexes are by EM or IF</p>
<p>Class III/IV</p> <p>Endocapillary proliferation</p> <p>Definitions are unclear and inconsistent. How many criteria are needed? Leukocyte influx only? Which inflammatory cell type? How much lumen reduction? Specific involvement of endothelial cells?</p> <p>Extracapillary proliferation</p> <p>Extracapillary cell proliferation involving less than 25% of the capsular circumference is not considered extracapillary proliferation</p> <p>Unclear how to incorporate these lesions in the segmental and global subdivision, because this subdivision is based on lesions within the tuft</p> <p>Lack of definitions for fibrocellular and fibrous crescents</p> <p>Extracapillary proliferation does not merely consist of proliferating cells</p> <p>Segmental and global lesions</p> <p>The validity of the subdivision can be questioned</p> <p>It is unclear what to do if exactly 50% of involved glomeruli have segmental lesions and 50% have global lesions; both of the definitions provided (IV-S if >50% segmental and IV-G if >50% global [in the text] or IV-S if ≥50% segmental and IV-G if ≥50% global [table 3 in refs. 1 and 2]) lack this provision</p>	<p>The term proliferation may not be appropriate to designate these lesions; consider avoidance of this term, redefine the characteristics of class III/IV lesions, consider separate definition for MPGN lesions, disentangling the mesangial and capillary wall changes of MPGN</p> <p>Redefine definition</p> <p>Redefine or remove segmental and global subdivision</p> <p>Provide definitions for these lesions</p> <p>Consider replacing the term proliferation with hypercellularity</p> <p>Option 1: maintain subdivision but clarify definitions</p> <p>Option 2: eliminate S and G subdivision and define an alternative subdivision that may achieve the goal of identifying the more vasculitic-like lesions in LN</p>

Table 1. Continued.

Topic and Concerns	Suggestions for Improvement
<p>Activity and chronicity</p> <p>It is unclear if a membranoproliferative pattern of injury is to be considered as active, chronic, or both</p> <p>Difficult to reliably distinguish between global sclerosis caused by LN or other causes</p>	<p>Decide whether double contours are indicative of activity or chronicity</p> <p>Redefine the role of global sclerosis in the classification</p>
<p>Class V</p> <p>Segmental scarring</p> <p>Difficult to reliably differentiate between segmental sclerosis as a consequence of class V LN and segmental sclerosis as a consequence of class III/IV LN</p>	<p>Redefine the role of segmental sclerosis in the classification</p>
<p>Other glomerular lesions</p> <p>Specific attention for other glomerular abnormalities occurring in the context of SLE is lacking</p>	<p>Consider including lesions, such as lupus podocytopathy, collapsing glomerulopathy, and TMA</p>
<p>Vascular lesions</p> <p>Vascular lesions should be graded into mild, moderate, or severe, but criteria for this grading are not provided</p> <p>Very little attention is given to vascular lesions occurring in the context of SLE</p>	<p>Define criteria for severity of vascular lesions (use <i>e.g.</i>, Banff guidelines)</p> <p>Consider including vascular lesions, such as immune complex deposition, lupus vasculopathy, TMA and vasculitis</p>
<p>Tubulointerstitial lesions</p> <p>There are no cutoff values provided for the reporting of severity of tubulointerstitial lesions; it is unclear if interstitial inflammation, tubular atrophy, and interstitial fibrosis need to be graded separately or if these can be combined into one or two parameters</p>	<p>Provide cutoff values: use, for example, Oxford IgAN classification guidelines</p>

EM, electron microscopy; IF, immunofluorescence; MPGN, membranoproliferative GN.

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