Histologic classification of glomerular diseases: clinicopathologic correlations, limitations exposed by validation studies, and suggestions for modification

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The value of classification systems applied to the examination of renal biopsies is based on several factors: first, on the ability to provide efficient communication between pathologists and between pathologists and clinicians; second, on the possibility to implement diagnostic information with prognostic indication. Even more important, the practical value of a classification is proved by the ability of providing elements that guide therapeutic decisions and can be used in the follow-up of the patient. With these aims, new histologic classification systems have been proposed in the last decade for lupus nephritis and IgA nephropathy under the leadership of the Renal Pathology Society and the International Society of Nephrology. These classifications have gained a significant level of worldwide acceptance and have been the subject of multiple single-center and multicenter validation studies, which have underpinned their clinical benefits and limitations and served to highlight remaining questions and difficulties of interpretation of the biopsy sample. More recently, a classification system has also been proposed for ANCA-associated crescentic glomerulonephritis (ANCA-GN), although the validation process for this is still in an early stage. In this review, we examine in some detail the ISN/RPS classification for lupus nephritis and the Oxford classification for IgA nephropathy, with emphasis on clinicopathologic correlations, their value for and evolving impact on clinical studies and clinical practice, and their significant limitations in this regard as exposed by validation studies. We also suggest possible ways by which these classifications might be modified to make them more applicable to clinical practice. Finally, we more briefly discuss the newly proposed classification for ANCA-GN.

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The value of performing a renal biopsy in a patient with suspected glomerular disease is twofold. First, of course, is to establish a diagnosis of a specific disease or category of disease, although in some cases this may be largely apparent from the patient's clinical history and serologic data. The latter is most often true with systemic diseases that frequently involve the kidney, such as systemic lupus erythematosus (SLE). The second, and perhaps more valuable to the clinician, is to provide prognostic information regarding the likely clinical course of the patient, and the likelihood of improving this prognosis with therapeutic intervention, most notably immunosuppressive therapy. For many glomerular diseases, although their identification on renal biopsy is generally straightforward, their histologic appearance on biopsy, much like their clinical presentation, can vary greatly. This histologic appearance represents a snapshot of prior and ongoing events within the kidney, and has been shown in studies performed over several decades to be correlated to some extent with both the clinical presentation and future events, including response to therapeutic intervention and likelihood of progression to end-stage renal disease (ESRD). It is for this reason that morphologic classification systems of several different glomerular diseases have been proposed, particularly those with the greatest degree of morphologic heterogeneity, including lupus nephritis (LN) and IgA nephropathy (IgAN). However, the value of these classification systems remains to be definitively established.

This value is dependent on a number of different parameters. First, the validity of any disease classification system

is based on the criteria of reproducibility (measured by the κ-value) and precision (which is the s.d. of variation), which ensure that a classification is widely applicable by pathologists around the world, with acceptably low intraobserver and interobserver variation, and necessarily implicate a level of simplicity that allows the classification to be applied within the context of routine clinical practice. Second and most important is the ability of the classification to provide prognostic information regarding the likelihood of disease progression, above and beyond the available clinical data at the time of biopsy and during follow-up, and/or to provide information useful in identifying those patients who are likely to respond to certain therapeutic interventions. Third, morphologic classification is a dynamic process, because periodic discoveries are made that add to our knowledge of etiology or pathogenesis, identify new markers of prognosis and/or therapeutic responsiveness, and identify new therapies. Thus, a widely applicable histologic classification system should truly be a working classification capable of undergoing modification in response to new knowledge without a significant loss of precision or ease of utilization. An example of the latter is the Banff working classification for renal allograft pathology, which over the past two decades has undergone key modifications in response to generation of new knowledge, such as the increased recognition of the importance of antibody-mediated rejection.[1–4]

Over the past decade, new histologic classification systems have been proposed for LN and IgAN under the leadership of the Renal Pathology Society (RPS) and the International Society of Nephrology (ISN). These classifications have gained a significant level of worldwide acceptance and have been the subject of multiple single-center and multicenter validation studies. More recently, a classification has also been proposed for antineutrophil cytoplasmic antibody (ANCA)–associated crescentic glomerulonephritis (ANCA-GN), although the validation process for this is still in an early stage. In this review, we will examine in some detail the ISN/RPS classification for LN and the Oxford (Mesangial hypercellularity, Endothelial hypercellularity, Segmental sclerosis, Tubular atrophy/interstitial fibrosis (MEST)) classification for IgAN. Particular emphasis is given to the results of validation studies of these classifications, and what these latter clinicopathologic studies tell us about the applicability and limitations of the classifications with regard to clinical studies and clinical practice. We will also more briefly discuss the newly proposed classification for ANCA-GN. It should be recognized that the prognostic precision of a classification applies to patients as a group but it can never predict what will actually happen in an individual patient. As such, biopsy data need to be combined with clinical and laboratory data when making therapeutic decisions in an individual patient.

LN: THE ISN/RPS CLASSIFICATION

The Systemic Lupus International Collaborating Clinics group recently revised and validated the classification criteria for lupus erythematosus.[5] Among these, a biopsy-confirmed nephritis compatible with LN, in the presence of lupus autoantibodies, is now considered to be a 'stand alone' criterion for SLE diagnosis because it is 'indisputably representative of the disease.' LN is actually very common among SLE patients, affecting 60 to 70% of this population, and continues to influence the prognosis of the disease, despite the introduction of more effective therapeutic schemes.

Three recent guidelines for the management of LN attempt to incorporate the best available evidence as well as expert opinion in an effort to help physicians dealing with these patients to make appropriate therapeutic choices. These guidelines are sponsored by the American College of Rheumatology (ACR),[6] the Kidney Disease-Improving Global Outcomes (KDIGO) working group,[7] and the Joint European League Against Rheumatism and the European Renal Association (EULAR/ERA-EDTA).[8] Each of these groups[6–8] substantiates the definitive adoption of the ISN/RPS classification of LN,[9] rather than the older World Health Organization (WHO) system.

The ISN/RPS classification of LN (Table 1) was proposed in 2003 by an international committee of renal pathologists, nephrologists, and rheumatologists, with the main purpose of reaching 'a consensus concerning the definition of the different classes of SLE nephritis and the meaning of the pathologic terminology applied, in order to standardize the way biopsies are interpreted and reported between different centers.'[9]

As has been described and commented on previously,[9–13] the major differences between the ISN/RPS classification and the previous 1995 WHO classification include the redefining of class I to include only biopsies with mesangial immune deposits, a substantial revision of classes III and IV, and a simplification of class V. Since the publication of the ISN/RPS classification, studies comparing this system with the WHO have consistently shown that the ISN/RPS classification is superior in terms of standardization and reproducibility of diagnosis among different centers. One of the largest analyses was conducted by Furness and Taub;[11] a total of 30 pathologists were involved to compare the ISN/RPS with WHO system in 20 cases of LN, and the ISN/RPS scheme obtained a significantly higher κ-value. Similarly, the studies conducted by Yokoyama *et al.*[12] and Grootscholten *et al.*[13] confirmed higher intraobserver and interobserver concordance using the ISN/RPS classification.

PROGNOSTIC VALUE OF THE ISN/RPS CLASSIFICATION

More conflicting results emerge from studies concerning the power of this classification in predicting disease outcome. Although the prognostic significance of renal biopsy findings is undisputable when nonproliferative (classes I, II, and V) and proliferative (classes III and IV) lesions are compared, less concordant data emerge from studies focusing on comparison between classes III and IV, on the outcome differences from the specification of active or chronic lesions, and from the evaluation of the predictive value of