The Kidney Biopsy in Lupus Nephritis: Past, Present, and Future

Samir V. Parikh, MD,[*] Anthony Alvarado, MD,[*] Ana Malvar, MD,[†] and Brad H. Rovin, MD[*]

Summary: Since its incorporation into clinical practice in the 1950s, the percutaneous kidney biopsy has played an important role in advancing our understanding of lupus nephritis (LN). The biopsy findings have been used to classify and subgroup LN in order to obtain an accurate diagnosis and also to inform treatment decisions and predict prognosis. Several classifications schemes have been applied clinically however despite this evolution in histopathologic classification, our ability to predict treatment response and determine prognosis remains limited. In this review we will examine the evolving role of the kidney biopsy in the management of LN, including the potentially larger role the biopsy could play in the future.
Semin Nephrol 35:465-477
Keywords: Lupus nephritis, kidney biopsy, systemic lupus erythematosus

The percutaneous kidney biopsy was adopted into clinical practice more than 60 years ago and the histologic patterns of lupus nephritis (LN) were described in the 1950s. Classification systems of LN based on these light microscopic patterns of injury were developed, first under the auspices of the World Health Organization (WHO of 1974, revised in 1982 and 1995), and then by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) of 2003. Besides an accurate diagnosis, the intention of classifying LN by histology was to provide a framework upon which to make treatment decisions and to define a patient's prognosis. Arguably, these goals are not being realized, especially in the context of the personalized medicine movement, and with the development of highly selective, targeted immunotherapies. In this review we examine the past and present roles of the kidney biopsy in the management of LN, and discuss the potentially larger role the biopsy could play in the management of LN in the future.

THE HISTOPATHOLOGICAL CLASSIFICATION OF LN

The aim of the ISN/RPS reclassification of LN histology was to better align biopsy findings to treatment options and prognosis than the WHO system (Table 1). Similar to the WHO system, the ISN/RPS is based on light microscopic findings. The ISN/RPS has attempted to distinguish more specifically between classes of proliferative LN by implementing a threshold system based on the level of glomerular involvement (Fig. 1).[1] Class III is defined as those biopsy specimens with less than half of their glomeruli affected by LN, whereas class IV biopsy specimens have 50% or more involvement. This sort of absolute criterion creates its own set of issues. Diagnostic accuracy becomes questionable when the total number of glomeruli in the specimen is low. It is not clear that there are true differences in disease pathogenesis or prognosis for the kidney between biopsy specimens showing levels of glomerular involvement near the cut-off value. For example, the clinical relevance of differentiating patients with 45% glomerular involvement from 55% glomerular involvement is questionable. In addition, the subcategories of global (G) and segmental (S) were added to describe proliferative LN (Fig. 1D and E) because there was evidence to suggest that global glomerular proliferation had a better prognosis when compared with segmental glomerular proliferation.[2] However, several subsequent studies have shown no significant differences in clinical outcome between global and segmental groups, at least in the context of current therapies.[3–5] Nonetheless, the clinical utility of these subgroups continues to be debated.

The ISN/RPS classification also created a more clear distinction between proliferative forms of LN and membranous (class V) LN (Fig. 1F). A simplified definition for class V LN was created that eliminated the subgroups for mesangial hypercellularity, focal proliferative, and diffuse proliferative LN that were present in the WHO classification. If a class V LN biopsy has evidence of active or chronic proliferative lesions, it now receives a diagnosis of class III or IV plus class V LN to emphasize the importance of recognizing and treating the (active) proliferative component because this has a more urgent impact on outcome.

An important deficit of the ISN/RPS system is its failure to account for tubulointerstitial lesions adequately. Moderate to severe interstitial inflammation is a risk factor for a poor long-term renal outcome (Fig. 1H).[6,7] Interstitial fibrosis and tubular atrophy

[*]*Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio.*
[†]*Nephrology Unit, Hospital Fernandez, Buenos Aires, Argentina.*
Financial disclosure and conflict of interest statements: none.
Address reprint requests to Brad H. Rovin, MD, Ohio State University Wexner Medical Center, Division of Nephrology, Medical Office Tower, Ground Floor, 355 W. 12th Ave, Columbus, OH 43210. E-mail: Rovin.1@osu.edu
0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2015.08.008

Table 1. Evolution of Lupus Nephritis Classification

Class	WHO Classification: 1974	WHO Classification: 1982	ISN/RPS Classification
I	Normal glomeruli	Normal glomeruli by LM, rare mesangial deposits by IF	Normal glomeruli by LM, mesangial deposits by IF
II	Mesangial disease	Mesangial disease Mesangial widening with mild hypercellularity Moderate hypercellularity	Mesangial disease Mesangial hypercellularity, matrix expansion, rare subendothelial or subepithelial deposits by IF, but not LM
III	Focal (<50%) disease	Focal segmental disease Active, necrotizing lesions Active and sclerosing lesions Sclerosing lesions only	Focal segmental or global disease involving <50% of all glomeruli III (A): active lesions III (A+C): active and chronic lesions III (C): chronic, inactive lesions
IV	Diffuse (≥50%) disease	Diffuse disease No segmental lesions Active necrotizing lesions Active and sclerosing lesions Sclerosing lesions only	Diffuse segmental (S) or global (G) disease involving ≥50% of all glomeruli IV-S: ≥50% glomeruli with segmental lesions IV-G: ≥50% glomeruli with global lesions IV-S (A), IV-G (A): active lesions IV-S (A/C), IV-G (A/C): active and chronic lesions IV-S (C), IV-G (C): chronic, inactive lesions
V	Membranous	Membranous Pure membranous GN Associated with class II Associated with class III Associated with class IV	Membranous May occur in combination with class III or IV; both are included in diagnosis
VI	N/A	Global glomerulosclerosis in ≥90% of glomeruli; no activity	Global glomerulosclerosis in ≥90% of glomeruli; no activity

Abbreviations: GN, glomerulonephritis; IF, immunofluorescence microscopy; LM, light microscopy.

more closely correlate with kidney function than glomerular lesions.[8–10] As suggested by Clark et al in this issue of Seminars (The Pathogenesis and Therapeutic Implications of Tubulointerstitial lesions in Human Lupus Nephritis), injury to the tubulointerstitial compartment may occur independently of the glomeruli in LN. Targeting treatment to the interstitium thus may become a relevant component of LN management in the future, and accurate classification of tubulointerstitial involvement will be necessary, including, but not limited to, characterizing the subsets of inflammatory cells infiltrating the interstitial space. Furthermore, new studies suggest that T and B cells within the interstitium, at least in some patients with LN, interact and may foster kidney-specific autoimmunity through the generation of kidney-specific autoantibodies.[11,12]

To supplement the WHO and ISN/RPS classifications, injury indices were developed, ostensibly to better forecast renal outcomes (Table 2).[1,13,14] The activity index (AI) represents the degree of inflammatory injury to renal parenchyma and generally comprises lesions that may be amenable to anti-inflammatory and immunosuppressive therapies (Fig 1B). The chronicity index (CI) represents the degree of chronic damage the kidney has sustained, and generally comprises lesions that are not currently thought to be reversible by known treatments (Fig. 1C). The reproducibility and clinical utility of these indices has been challenged,[15,16] and other investigators have modified the original indices into complex algorithms thought to better predict renal survival, but with limited clinical applicability.[17]

The ability of the light microscopy–based LN classifications, with or without a version of activity and chronicity scores, to predict kidney outcomes of patients remains controversial. Many of the studies performed to evaluate this question were conducted before the ISN/RPS system was in place. For the most part, these studies showed that adding information from the WHO classification did not predict outcomes better than what could be predicted by clinical metrics alone.[18,19] Some investigations found that considering histologic features of chronic kidney injury with clinical biomarkers such as an increased serum creatinine concentration helped predict long-term kidney function.[13] Other studies have suggested that a high level of inflammatory activity in the biopsy specimen, such as the presence of glomerular fibrinoid necrosis and cellular crescents, or a high degree of chronic renal damage, reflected by a chronicity index greater than 3, predicted an unfavorable prognosis.[13,19,20]