

The Holy Grail: Pathological indices in lupus nephritis

Interpretation of renal biopsies from patients with systemic lupus erythematosus (SLE) is complicated by the marked variability of the pathology. The nature and the distribution of the glomerular lesions vary among patients, among the glomeruli within a biopsy, and even within individual glomeruli. SLE is a chronic disease, and the glomeruli often show both acute inflammation and scarring. In addition, SLE tubulointerstitial and vascular pathology may accompany the glomerular lesions. Despite the many pathological permutations, the very first renal biopsy study in patients with SLE demonstrated that outcome was a function of the extent of glomerular inflammation [1]. Confirmation of this seminal observation and the contributions of many nephrologists and renal pathologists culminated in the World Health Organization (WHO) Classification of SLE Glomerulonephritis in 1982 [2]. The WHO classification is easily learned, readily performed and reproducible, and it has become the standard method by which the pathologist communicates the extent and severity of glomerular pathology to the nephrologist. Because the prognosis is related to the WHO Class of glomerular disease [3], the renal biopsy serves as a guide for the clinician concerned with therapy for the SLE patient with renal involvement [4].

Despite its success in defining the classes of glomerular disease that require therapy, the WHO Classification does not identify which patients with segmental glomerulonephritis, diffuse glomerulonephritis, and mixed membranous and proliferative lesions will develop progressive renal disease. Admittedly, the simplicity of the WHO Classification ignores the individual histological components of the acute inflammatory lesion, does not quantify the extent of glomerular inflammation and scarring, does not separately categorize lesions which are more characteristic of a protracted clinical course, and does not include tubulointerstitial and vascular pathology. It has been suggested that a more inclusive and quantitative pathological analysis might improve the prognostic power of the renal biopsy. Conrad Pirani, the renal pathologist for many of the early, influential clinicopathological studies of lupus nephritis, and his clinician colleagues [1, 5] developed a semiquantitative method for analyzing renal biopsies because “it compels the patholo-

gist to examine in detail each individual histologic feature,” and they developed a scoring system and lists of “active” (potentially reversible acute inflammation) and “inactive” (irreversible scars) lesions [5]. In subsequent analyses, indices of renal pathology were created from the semiquantitative scores, and the activity (AI) and chronicity (CI) indices developed by Austin et al are the most widely accepted and influential [6, 7]. However, histological indices have been criticized because the AI does not predict outcome, and study of the CI yields mixed results, with some investigators finding them prognostically useful while others find that they do not predict outcomes [reviewed in 8]. Although they are unable to define a score that has the sensitivity and specificity to reliably identify patients who will subsequently develop progressive renal disease [3], the AI and CI may find application as pathological summaries [6, 7].

In the current issue of *Kidney International*, Hill et al attempt to improve upon the information revealed by a renal biopsy of SLE nephritis by utilizing a more detailed histological analysis [9]. Their model comprises the sum of four indices: the glomerular activity index, modified from the AI of Austin et al [6, 7] adds the presence of glomerular monocytes while eliminating interstitial inflammation; the tubulointerstitial activity index includes histological signs of tubular injury and interstitial inflammation but excludes tubular atrophy; the chronic lesions index, modified from the CI of Austin et al [6, 7], includes both glomerular sclerosis and tubular atrophy; and the immunofluorescence index is based on semiquantitation of immunofluorescence staining. In developing the index the authors demonstrated correlations among the morphological features, the component indices, and the clinical parameters that imply that the assignment of the histological elements to the component indices is valid and that the indices reflect the underlying pathogenetic mechanism. In addition, significant correlations were observed between the biopsy index and the clinical parameters at the time of the initial biopsy and at the protocol biopsy performed six months later, and these correlations were higher than for the predecessor indices. The study also sought to optimize correlations between the biopsy index and study outcomes at the time of the initial biopsy and in biopsies following treatment. Although weak correlations were observed between the biopsy index and the study outcomes at the time of the first biopsy, at the protocol biopsy performed after treatment,

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correlations between the biopsy index and the final serum creatinine, end-stage renal disease, and doubling of the serum creatinine were statistically significant and much stronger than before. Despite the apparent improvement, the correlations between the biopsy index and outcome and the predecessor indices and outcome were not significantly different. It is apparent that the WHO Classification does not utilize all available information in the renal biopsy, but the present study demonstrates that a detailed pathological analysis, using all available morphological data, does not improve upon either the diagnostic or prognostic value of the histological (WHO) classification at the time of the initial biopsy.

The improved correlation of the biopsy index with the study outcomes seen at the time of the second biopsy merits further comment: The biopsy index and, importantly, its component indices that reflect active glomerular inflammation and immune complex deposition, correlate with doubling of the serum creatinine, final renal function and end-stage renal disease. This focus on active, potentially reversible pathology that persists after therapy and not on signs of irreversible nephron loss and scarring suggests that the biopsy index may have a role in evaluating the response to treatment. However, there is a caveat: the reported correlations were for a group of patients, and the present study does not demonstrate that the biopsy index can or should be applied to individual patients for the purpose of predicting the outcome. In any case, the limitation in caring for patients with lupus nephritis is not only identification of those with the worse prognosis. In fact, all 18 patients in this study who doubled their serum creatinine despite "induction therapy" had diffuse lupus glomerulonephritis (WHO Class IV), and given the natural history of untreated lupus glomerulonephritis [4], those with comparable glomerular pathology who did not progress should be considered therapeutic remissions. Current treatment of lupus glomerulonephritis, that narrowly focuses on anti-inflammatory drugs and immunosuppressive agents, is a more pressing problem for the clinician whose patient

with lupus nephritis has a suboptimal response to therapy. As new approaches are developed, morphologic methods, such as the index proposed by Hill et al [9] that focus on reversible pathology and specific pathogenic mechanisms, may be helpful in evaluating therapeutic efficacy. One must concur with the authors that "the greatest value of the new biopsy index will lie in the systematic evaluation of entire series of patients" and not in the identification of individuals at risk of adverse outcomes.

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