The Pathogenesis and Therapeutic Implications of Tubulointerstitial Inflammation in Human Lupus Nephritis

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Summary: Nephritis is a common complication of systemic lupus erythematosus for which current therapies often prove inadequate. Current lupus nephritis classification systems emphasize glomerular acuity and scarring. However, tubulointerstitial inflammation (TII) and scarring are much better predictors of progression to renal failure. It now is becoming clear that the immunologic features, and probable underlying mechanisms, are very different in lupus glomerulonephritis and TII at the time of biopsy. Although glomerulonephritis is a manifestation of systemic autoimmunity, TII is associated with local in situ adaptive immune cell networks predicted to amplify local inflammation and tissue damage. In addition, poorly defined networks of innate immune cells and effectors likely contribute to the severity of local inflammation. Defining these in situ immune mechanisms should lead to a better understanding of prognostically meaningful lupus nephritis subsets and show novel therapeutic opportunities.
Semin Nephrol 35:455-464
Keywords: Lupus nephritis, tubulointerstitial inflammation, adaptive immunity, innate immunity

The most common and severe manifestation of systemic lupus erythematosus (SLE) is certainly lupus nephritis.[1–5] Up to 60% of SLE patients develop lupus nephritis, with most of these patients requiring major immunosuppressive therapies such as cyclophosphamide or mycophenolate mofetil.[6–9] However, despite aggressive treatment, up to 50% of lupus nephritis patients progress to renal failure within 5 years of diagnosis.[10–12]

Ethnicity is a major determinant of renal failure risk, with African Americans and Hispanics having a worse prognosis than Caucasians.[11,13] Reflecting their worse prognosis, and possibly differing responses to therapies, the treatment recommendations for African Americans and Hispanics are different than those for Caucasians and Asians.[9] It is not entirely clear, however, if African Americans and Hispanics have a higher ultimate risk of renal failure or if they just progress to renal failure more quickly. Most studies showing the risk associated with ethnicity are 5 years or less in duration. However, at least one study suggested that patients continue to progress to renal failure beyond 5 years.[14] In this Danish study, less than 20% progressed in 5 years, although approximately 50% were in renal failure 25 years after diagnosis.

These more recent epidemiologic studies all have been performed in the modern era of treatment in which cyclophosphamide and/or mycophenolate mofetil were the standards of care. Although these drugs are clearly effective in some patients, short-term response rates have not improved appreciably since the introduction of cyclophosphamide for lupus nephritis in the 1980s.[14–16] Therefore, either rapidly or eventually, half of lupus nephritis patients fail these modalities and progress to end-stage kidney disease.

The need for both more effective and less toxic therapies in lupus nephritis is obvious and pressing. However, it is unclear which therapies to pursue and in which subpopulations of lupus they might be efficacious. We suggest that this uncertainty in how to proceed reflects limitations in both our understanding of lupus nephritis and in how we classify patients and assign prognosis.

PROGNOSTIC VALUE OF RENAL BIOPSIES

The current standard is to perform a biopsy on all SLE patients who present with active urinary sediment and/or more than 500 mg/protein in 24 hours.[9,17] Lupus patients then are categorized broadly as having either proliferative or nonproliferative nephritis based on the activity and frequency of glomerular lesions, with therapeutic decisions based on this classification. However, current histologic measures of disease activity, which emphasize glomerular involvement, perform poorly in identifying those patients at risk for subsequent renal failure.

The most commonly used classification system reflects this focus on glomerular inflammation. The 2003 International Society of Nephrology/Renal Pathology Society[18] lupus nephritis classification focuses

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Financial support: Supported by the University of Chicago Autoimmunity Center of Excellence (U19AI082724) and NIDDKRO1-AR55646.

Conflict of interest statement: none.

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0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2015.08.007

exclusively on histologic changes of the glomerulus. Similarly, the National Institutes of Health activity index quantifies the severity of lupus nephritis and is scored using six pathologic features, of which five involve the glomerular compartment, with 21 of the 24 activity points awarded based on glomerular findings.[13,19] However, the prognostic value of glomerular inflammation, at best, remains unclear.

Several studies have shown that glomerular measures of disease activity do not accurately predict the subsequent clinical course.[12,13,19–23] For the most part, these studies were performed during the modern era when all patients received cytotoxic therapies. Earlier studies clearly showed that patients with proliferative nephritis have a worse prognosis than patients with nonproliferative nephritis. and that this group does better with immunosuppressive treatment.[24] However, in these earlier studies, other features of the biopsy, such as tubulointerstitial inflammation, were not assessed systematically. Furthermore, features predictive of resistance to immunosuppressive therapy were not analyzed.

Several studies in the immunosuppressive era of lupus nephritis treatment, extending back to the 1980s, have indicated that tubulointerstitial inflammation is prognostically more meaningful than glomerular inflammation and is more likely to be correlated with increased creatinine level at the time of biopsy and with risk for subsequent renal failure.[13,22,25–28] Many of these studies noted that more active tubulointerstitial inflammation (TII) tended to be associated with active glomerulonephritis (GN). However, multivariate analysis showed that TII was an independent predictor of progression to renal failure[13] and correlated with serum creatinine level at the time of biopsy.[13,26] Furthermore, TII is not associated with low complement levels, or high titers of double-stranded DNA (dsDNA) antibodies,[13,26] factors epidemiologically and mechanistically tied to GN. Therefore, TII is an independent and important predictor of renal failure in lupus nephritis.

The current assessments of TII are largely qualitative, with severity scored as the fraction of the tubulointerstitium infiltrated with inflammatory cells on periodic acid–Schiff–stained paraffin-embedded sections. By simply staining with anti-CD45 antibodies, and assessing the fraction of the tubulointerstitium infiltrated with $CD45^+$ cells, intermediate grades of TII can be assessed more accurately, which are prognostically significant.[13]

Although the degree of TII is prognostically more important than GN activity, it is not clear how this information should inform therapy. Clinical trials have not been stratified by TII and therefore it is not clear if one therapy is relatively more effective in TII. However, the fact that severe TII predicts renal failure in all lupus patients suggests that all current therapies are relatively ineffective for this manifestation.

In contrast to commonly used indices of active glomerular inflammation, indices of scarring (glomerulosclerosis, interstitial fibrosis, and tubular atrophy) are strongly predictive of subsequent renal failure.[13,22,26,29,30] The National Institutes of Health chronicity index is a composite score that equally reflects scarring in both the glomeruli and the tubulointerstitium. However, prognostic value of the chronicity index lies primarily in those components that capture interstitial scarring.[13] Measures of glomerular scarring do not provide independent prognostic information to the chronicity index. In other renal diseases, interstitial scarring also identifies patients with a poor prognosis.[31] In IgA nephropathy, which primarily is considered to be a glomerulonephritis, tubular atrophy and interstitial fibrosis are more predictive of subsequent renal insufficiency than segmental glomerulosclerosis.[32]

There is substantial evidence that inflammation leads to fibrosis. This central idea is an extension of the known roles of both inflammation and fibrosis, in the normal processes critical for organ repair after injury. Macrophages play a role in both processes,[33] and ablation of macrophages mitigates fibrosis.[34–36] Furthermore, the extent of macrophage infiltration correlates with the extent of fibrosis.[37] Therefore, the overall effect of macrophages in these model systems appears to be to promote fibrosis. However, infusion of M2 macrophages, which act to limit inflammation, attenuate renal fibrosis in mice.[38] Adaptive immunity appears important because deletion of Rag, thereby eliminating both B and T cells, can protect against renal fibrosis but not, interestingly, GN.[39] Furthermore, T cells are required for fibrosis after ischemia-reperfusion injury.[40,41] However, it is not clear that monotherapy targeting adaptive immunity, or inflammation, will be sufficient to prevent fibrosis in most patients.

THE PATHOGENESIS OF TUBULOINTERSTITIAL INFLAMMATION

Although GN is a manifestation of systemic autoimmunity,[42–44] lupus TII has histologic features suggesting that local in situ immunity might contribute to, and propagate, local tubuloinflammation and organ damage.[45,46] What is most striking is how different the inflammatory infiltrates are in glomerular inflammation and TII. In lupus glomeruli, the degree and type of involvement varies with International Society of Nephrology/Renal Pathology Society class. In nonproliferative lupus nephritis (classes I and II), patients have immune complex deposits in the mesangium,