Understanding Histolopathologic Characteristics to Predict Renal Outcomes in Lupus Nephritis

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In this issue of the Clinical Journal of the American Society of Nephrology, Rijnink et al. (1) present the results of a single-center retrospective study of clinical and histopathologic predictors of renal flare and ESRD in patients with lupus nephritis. The cohort was 105 patients with lupus nephritis accrued between 1987 and 2011 and followed for a median of 9.9 years; 47 patients experienced renal flare, and 21 patients developed ESRD. Among the clinical predictors, nonwhite race was associated with both renal flare and ESRD; eGFR was also identified as a predictor for ESRD. Presence of fibrinoid necrosis was the predictor of both renal flare and ESRD, and fibrous crescents and interstitial fibrosis/tubular atrophy were additional predictors of ESRD. It is important to note that 91 of 105 patients were classified as class III or IV lupus nephritis. Although there was no relation between the class of lupus nephritis and renal survival, classes of lupus nephritis were associated with eGFR during follow-up. The authors suggest that their histopathologic prognostic factors should be validated and (if validated) included in a new histologic classification of lupus nephritis (1).

Undoubtedly, International Society of Nephrology/Renal Pathology Society classification of lupus nephritis may be too glomerulocentric and concentrated only on the evaluation of endocapillary (compared with extracapillary) proliferation; there is sufficient evidence that classes I, II, and V do have better outcome compared with classes III and IV (what was previously called proliferative lupus nephritis). Because almost 90% of patients included to the study by Rijnink et al. (1) had class III or IV, their study can only show that the outcome of different subclasses of proliferative lupus nephritis may not be very much different. Furthermore, in patients with classes III and IV, other parameters, such as fibrinoid necrosis, fibrous crescents, and tubular atrophy/interstitial fibrosis, provide additional prognostic information.

Tubulointerstitial fibrosis is a well known predictor of the outcome in most CKDs, including lupus nephritis. Three recent retrospective studies from China have also identified tubulointerstitial and renal vascular lesions and glomerular crescents in patients with lupus nephritis as predictors of renal outcome (2–4). The study by Rijnink et al. (1) performed in a multiethnic population (mostly [65%] white) confirms some of the findings from the prior studies from China and identifies some new putative prognostic factors, namely fibrinoid necrosis and more specifically (compared with ref. 4), fibrous crescents.

The main limitation (as for the evaluation of histologic data) is that the study is relatively small and as also stressed by the authors, could not assess the prognostic value of some rarely occurring events, such as hyaline thrombi and karyorrhexis. Because a large proportion of examined patients had class III or IV lupus nephritis, it was also not possible to define putative early histopathologic predictors of progression from class II to class III/IV (possibly related to the early increase of proteinuria), which may be very different from the predictors of progression to ESRD. These limitations argue for the need for a much larger multicentric study with a more representative inclusion of patients with classes II and V lupus nephritis, which has been already done in IgA nephropathy. In the Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA) Study, in 1147 patients with IgA nephropathy, tubular atrophy/interstitial fibrosis was the best predictor of the loss of eGFR, but endocapillary proliferation was identified as an early marker of progression from microscopic hematuria only to proteinuria.

An additional consideration is that the study cohort comprised patients accrued over a very long period; some of them were treated with induction treatment with azathioprine only, which has been shown to be less effective, even in terms of the accumulation of chronic changes on the second biopsy (5). Treatment of patients over the study period has changed considerably, and patients are now treated in the induction phases with lower doses of cyclophosphamide or oral mycophenolate mofetil, with significant improvement in their outcomes (6).

Other investigators have identified additional clinical predictors, such as partial remission, which has been shown to be associated with better outcome and renal survival compared with nonresponse in patients with severe lupus nephritis, and an early response of proteinuria was a good markers of long-term prognosis in patients with proliferative lupus nephritis. Recent analysis of data on long-term outcomes from the Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis (MAINTAIN) Trial identified proteinuria cutoff of 0.7 g/d at 12 months as the best predictor of renal outcome in (mostly) proliferative lupus nephritis (7). Anti-C1q antibody positivity (especially if combined
with the presence of anti-double-stranded DNA and low C) was also shown to be tightly related to not only the presence and activity of proliferative lupus nephritis but also, renal flares. It seems probable that, in the near future, evaluation of the activity of lupus nephritis and prediction of its outcome will be further improved with the use of noninvasive biomarkers, including urinary proteomics and metabolomics. Combinations of different urinary biomarkers (including hepcidin, monocyte chemoattractant protein-1, and hemopexin) predict the extent of interstitial inflammation and interstitial fibrosis. Combinations of liver fatty acid binding protein, monocyte chemoattractant protein-1, albumin, and transferrin have been associated with a better outcome in patients with lupus nephritis (8).

It is imperative that, in general, histopathologic parameters at the time of diagnosis improve the prediction of the outcome on the basis of the clinical and laboratory data obtained at presentation alone and 1 year after the start of the treatment. Until now, all patients with class III/IV lupus nephritis were treated with the same induction and maintenance treatment; early identification of patients at high risk of progression to ESRD could substantiate more aggressive approach (e.g., multitarget treatment) in this high-risk subgroup if such an approach is shown to result in improved outcome in a randomized, controlled trial. There is a general consensus that renal biopsy at presentation is of utmost importance for the diagnosis of the specific class of lupus nephritis, but its contribution to the prediction of outcome and response to treatment is controversial. There may be, moreover, a discrepancy between clinical and histologic remission, with persisting activity and accumulating damage even in patients in complete clinical remission. Second renal biopsy after 6 months of therapy has been shown to be more predictive of outcome compared with initial biopsy and should probably be considered at least in nonresponding patients (9). Evaluation of the kidney biopsy could also benefit from the more detailed analysis of infiltrating cell populations. CD163+ M2c-like macrophages are most prevalent in renal biopsies of patients with lupus nephritis and correlated with the activity score in the biopsy. Moreover, macrophage subpopulations were able to distinguish between class IV and other classes of lupus nephritis, and renal function at the time of biopsy correlated with overall number of infiltrating macrophages. Urinary soluble CD163 was shown to reflect glomerular inflammation in patients with lupus nephritis (10). Prediction of renal outcome on the basis of renal biopsy can be further substantially improved looking at the intrarenal expression of different genes with complete response clustering with the expression of IFN pathway genes and nonresponse being associated with the expression of C genes (11).

In conclusion, histopathologic classification of lupus nephritis should also take into consideration (at least) fibrinoid necrosis, crescents, and tubular atrophy/interstitial fibrosis. Similar to the VALIGA Study, in patients with IgA nephropathy, a large multicenter, multiethnic cohort of patients with different classes of lupus nephritis with prospective follow-up should be formed to validate data coming from relatively small studies limited to only some ethnic subgroups. Newer methods of evaluation of biopsy samples, including the analysis of infiltrating cells and possibly, gene expression of some proteins involved in immune response, could also contribute to better prediction of renal outcome. Availability of urinary samples from the time of biopsy could enable us to evaluate the putative noninvasive biomarkers of activity and predictors of outcome (possibly measured at several time points during follow-up). All of these developments hold the potential to improve our assessment of the activity and the outcome of lupus nephritis, with the aim at more targeted and personalized treatment. The study by Rijnink et al. (1) is thus a small step on the long way but in the right direction.

Disclosures
None.

References

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