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Beyond clinicopathologic correlations in lupus nephritis: Future lies in molecular-based composite classification

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Clinicopathologic correlations in lupus nephritis (LN) have traditionally provided the basis for pathologic classification of the disease on renal biopsy. However, these correlations are not perfect. Although renal biopsy is considered the gold standard for diagnosing and classifying LN, it suffers from inherent shortcomings and drawbacks. The currently used ISN/RPS classification is mainly based on morphology and is glomerulocentric in outlook. Given the imperfections of ISN/RPS classification of LN, the future lies in the integration of traditional morphology with clinical, genetic and molecular markers to classify the disease more accurately and make the biopsy report more informative for choosing best treatment, to predict the response to treatment and to prognosticate the course of disease in an individual patient.

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Commentary

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with varied presentations and a relapsing and remitting clinical course. It typically involves skin, joints, serosal membranes and blood, but can affect almost any organ or tissue in the human body. Kidney involvement in SLE is one of its most dreaded complications and is termed lupus nephritis (LN). It occurs in about 50%-60% of cases of SLE, usually within the first year of diagnosis and is the major cause of morbidity and mortality in these patients (1). LN, like SLE, has varied clinical presentations (from asymptomatic to very severe life-threatening renal failure) and a myriad of lesions on renal biopsy. In fact, LN has the broadest range of morphological alterations on renal biopsy not paralleled by any other single kidney disease. LN tends to be more severe in children, males and individuals of African descent. While LN is often suspected on clinical grounds or laboratory investigations, it can only be confirmed on renal biopsy. Thus, renal biopsy plays a crucial role in the diagnosis, management and prognosis of LN (2). It is not only necessary to confirm the diagnosis of LN, it is equally or even more important to categorize or classify LN and to quantify acute or chronic damage on renal biopsy to guide treatment, monitor the effect of therapy and offer prognostic information. Hence, repeat biopsies are common in LN (2,3).

While renal biopsy is currently the gold standard for diagnosing, classifying and quantifying renal damage in LN, it has some inherent limitations. Sampling error is common to all needle biopsies of human organs. The experience and expertise of the reporting pathologist is also of utmost importance. Intra-observer and inter-observer variability is a significant problem in the worldwide application of pathologic classifications. Boundaries between various classes are arbitrary and the thresholds for classifying many lesions not completely evidence-based (4,5).

In this issue of *Journal of Nephropathology*, Owji et al have analyzed the clinical and laboratory features in a large cohort of 496 cases of LN (over a period of 16 years) from Shiraz University of Medical Sciences, Iran and correlated these with the pathologic classes of LN (6). They found

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fair correlation of some clinical and laboratory features with some classes of LN. However, it is well known that the correlation between clinical and laboratory features and the pathological features on renal biopsies is not perfect in LN, as in many other renal diseases (7). Despite this fact, such clinicopathologic studies are very important in shedding light on the differences or heterogeneity of disease in different populations, countries, or races. These differences may reflect differences in the biopsy policy or work up of biopsies, or true differences in the patterns of disease. The later may again be due to differences in the environmental or genetic factors. A similar but smaller study (n=71) on clinicopathological correlations in LN was conducted by Shariati-Sarabi et al also from Iran (8). There are many similarities in the two studies.

The strengths of the study under discussion include a large sample size, a homogeneous population of affected patients and the use of electron microscopy (EM) in all cases, which is not widely available in most developing countries. The authors have emphasized the use of EM as the most powerful tool for the classification of the disease. However, it is well established that the bedrock of the currently used ISN/RPS classification is morphology or LM supported by immunofluorescence (IF). EM is not the mainstay for classification of LN. In fact, its use is complimentary and still optional in ISN/RPS classifications, including the latest revised classification (7-11).

The study has some limitations too as acknowledged by the authors. The main limitations include its retrospective design, and a lack of data on the treatment or follow-up and prognosis of the disease. National Institutes of Health (NIH) activity and chronicity indices were also not analyzed in this study. According to some investigators, these are very important, even more important than the classes of LN, and should be part of the report.

It is clear that ISN/RPS classification of LN is not perfect. It does not completely reflect the underlying spectrum of pathophysiological mechanisms of LN. It is mainly glomerulocentric in nature. Although the revised classification has included activity and chronicity indices of NIH, which address the changes in the tubulo--interstitial compartment, the vascular lesions are still not formally included in the classification (11). Given these shortcomings and imperfections, the future lies in the integration of traditional morphology with clinical, genetic and molecular markers to classify the disease more accurately and make the biopsy report more informative for choosing best treatment, to predict the response to treatment and to prognosticate the course of disease in an individual patient (12).

In summary, Owji et al deserve compliments on sharing their experience of clinicopathologic correlations in a large, racially homogeneous population of LN from Iran. This cohort may form the starting point for outcome and prognostic studies and in future, the molecular investigations to increase our understanding of complex disease of LN.

Author's contribution

MM is the sole author of the paper.

Conflicts of interest

The author declared no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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