



The underestimated significance of nonproliferative lupus nephritis

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Lupus nephritis (LN) is the most common type of immune complex-mediated organ damage in systemic lupus erythematosus (SLE) and is an important cause of long-term disability and death [1]. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classifies the pathological findings of LN into six classes [2]. Excluding advanced sclerosing LN (class VI), the remaining LN classes are classified as proliferative (classes III and IV) and nonproliferative (classes I, II, and V) based on the glomerular findings. Unlike proliferative LN, which has a poor prognosis and requires more aggressive treatment with immunosuppressive drugs, nonproliferative LN has relatively good renal outcomes [3,4] and is not routinely treated with immunosuppressive drugs [5]. Therefore, nonproliferative LN has received relatively less attention than proliferative LN, and there are few reports on the long-term renal outcomes of nonproliferative LN.

In this issue of the *Korean Journal of Internal Medicine*, Kang et al. [6] report their findings on the long-term renal outcomes and prognostic factors in a retrospective cohort with only nonproliferative LN. They showed that 29.6% of the patients followed for a median of 103 months had poor renal outcomes, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m². They also found that older age, low eGFR at 6 or 12 months, failure to reach complete remission at 6 months, and activity score > 6 or chronicity score > 4 were significantly associated with poor renal outcomes in univariate analyses, while only a low eGFR at 6 months was significantly associated with poor renal outcomes in multivariate analysis (hazard ratio 0.974, 95% confidence interval 0.953–0.995; $p = 0.017$). They demonstrated that contrary to previous assumptions, patients with

nonproliferative LN had poor renal outcomes in long-term follow-up, particularly those with a low eGFR after 6 months of treatment.

This study is interesting from several perspectives. First, the authors analyzed the renal outcomes and prognostic factors of all nonproliferative classes of LN, not just one [6]. Nonproliferative LN includes both mesangial types (classes I or II) and purely membranous type (class V) [2]. Because not all of these types of LN tend to have a poor prognosis [3,4], they are grouped into one category and recent practice guidelines recommend the same treatment strategy. Only the membranous type with nephrotic range proteinuria or patients who do not respond to an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker are routinely treated with cytotoxic agents [5]. Unlike assessments that have been made by grouping prognosis and treatment strategies, few studies of long-term renal outcomes have examined all types of nonproliferative LN [7,8]. In this study, based on a relatively large population, the prognosis of nonproliferative LN was poor, contrary to previous assumptions. Kang et al. [6] found that in four out of seven patients who underwent repeated biopsy, the disease transformed into proliferative LN. Because this is in the same context as other studies [3], additional research should determine whether such transformation is associated with the poor outcomes of nonproliferative LN.

Second, Kang et al. [6] set “eGFR < 60 mL/min/1.73 m²” as a long-term renal outcome, and this signifies progression to chronic kidney disease (CKD). Most studies of LN outcomes have set creatinine doubling, end-stage renal disease, and mortality as outcomes. However, as with other renal diseases, CKD itself is an important risk factor for morbidity and mortality in SLE patients [9], and there is growing interest in the progression of LN patients to CKD. Two recent studies

analyzed the CKD progression rate and predictors for Korean patients with all classes of LN: in one study, 29.1% of the patients progressed to CKD during a median follow-up of 131 months [10]; in the other, 20.5% of the patients progressed to CKD during a mean follow-up of 48 months [11]. Because 29.6% of the patients progressed to CKD during a median follow-up of 103 months in Kang et al. [6], which targeted only patients with nonproliferative LN, it would be difficult to say that the prognosis of these patients is not as good as previously known. Unlike the two studies that reported that a decrease in eGFR at the time of LN diagnosis predicted a poor renal outcome, Kang et al. [6] found that a decrease in eGFR after 6 months of treatment, rather than at the time of diagnosis, predicted a poor renal outcome.

In conclusion, this article provides important clinical information that, unlike previous assumptions, indicates that a significant number of nonproliferative LN patients have poor renal outcomes, particularly those with a decreased eGFR after 6 months of treatment. Therefore, when we encounter these patients in clinical practice, we should monitor them carefully and consider more aggressive treatment.

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