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Editorial

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Exploring complement activation as a therapeutic target in lupus nephritis

Beom Jin Lim[1]

[1]Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea

See "Clinicopathological differences in the activation pattern of the complement system between pediatric and adult lupus nephritis: a single centered retrospective study in Korea" by Park et al. on page 24, Vol. 29, No. 1, 2025

Lupus nephritis is one of the most serious manifestations of systemic lupus erythematosus (SLE) [1]. Despite advances in immunosuppressive therapies, lupus nephritis continues to be a significant clinical challenge, partly due to the incomplete understanding of its underlying pathogenic mechanisms. The complement system, a component of innate immunity, is activated by immune complexes and plays a role in tissue damage associated with lupus nephritis [2].

The complement activation pathway in lupus nephritis has been the subject of extensive investigation for several decades [3]. All three activation pathways—the classical, alternative, and lectin pathways—participate in the tissue injury of lupus nephritis [2]. In standard clinical practice, serum levels of complement component (C)3 and C4, along with the tissue deposition of C3, C4, and C1q, have been used as markers indicative of abnormal complement activation. The total hemolytic complement activity (CH50) assay has been used as a functional evaluation of the complement system. In addition to these conventional assays, various complement split products, including inactivated C3b, C3dg, C3d, C4d, and C5a, can be detected in both blood and urine specimens [4]. Recent technological advancements have significantly enhanced our understanding of complement activity. For example, cell-bound complement activation products, which are measured by quantitative flow cytometry, have been identified as more sensitive indicators of SLE compared with traditional complement measurements [5]. Furthermore, the advent of next-generation sequencing techniques, such as whole-genome and whole-exome sequencing, has facilitated a more comprehensive exploration of the pathogenesis of SLE. These investigations have also uncovered that mutations and copy number variations in genes associated with the complement pathway play a role in the etiology of SLE [6,7].

In a previous issue of *Childhood Kidney Diseases*, Park et al. [8] conducted an analysis comparing complement activation patterns in pediatric and adult patients diagnosed with lupus nephritis. Their findings indicated that pediatric patients exhibited significantly lower serum C3 levels and less tissue-bound C4d intensity, despite the fact that both cohorts presented similar histological classifications by the International Society of Nephrology/Renal Pathology Society classification. Although this study utilized a single-center, retrospective analysis design and focused on a limited range of serum and tissue-bound complements, the results imply the existence of distinct pathophysiological mechanisms across different age groups, potentially influencing age-dependent prognosis. The discovery of differing levels of glomerular C4d intensity between pediatric and adult patients is quite interesting. Many studies have investigated C4d expression in the glomerulus and peritubular

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Correspondence to
Beom Jin Lim
Department of Pathology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
E-mail: bjlim@yuhs.ac

capillaries in biopsies of lupus nephritis. Although the results have varied, several studies have found a correlation between glomerular C4d expression and disease activity represented by the activity index [9]. The observed difference in C4d intensity between pediatric and adult patients, despite no variation in the activity index, suggests that the underlying pathophysiological mechanisms may differ between these age groups. To confirm this, larger multi-center studies will be necessary. However, challenges such as variations in C4d staining methods [10]—immunohistochemistry versus immunofluorescence—and the absence of standardized criteria for assessing intensity may hinder the execution of such studies.

The emphasis on complement activation in the context of lupus nephritis is motivated not only by academic interest in revealing the disease's pathogenesis and underlying mechanisms, but also by clinical needs. The recent advancements in the development of complement inhibitors, which specifically target various stages of complement activation, represent a novel therapeutic strategy for conditions such as C3 glomerulopathy, atypical hemolytic uremic syndrome, immune complex-mediated membranoproliferative glomerulonephritis, and anti-neutrophil cytoplasmic antibodies-associated glomerulonephritis [11]. Although these complement inhibitors have yet to be employed in the treatment of lupus nephritis, it has been reported that a complement factor B inhibitor significantly improved renal function and biopsy findings in an animal model of lupus nephritis (MRL/lpr mice) [12]. The application of complement inhibitors in the context of lupus nephritis is gaining momentum due to the advancement of personalized medicine. Thorough assessments of complement activation status in individual patients may facilitate the development of more effective intervention strategies tailored to each patient.

In conclusion, elucidating the complexity of complement activation in lupus nephritis is both a scientific imperative and a clinical opportunity for developing new therapies. Enhanced understanding of complement activation in lupus nephritis will facilitate the more precise deployment of newly developed complement inhibitors. This evolution in therapeutic strategy necessitates the adoption of more comprehensive complement analysis methodologies than those currently in use.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

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Data availability statement

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