Editorial

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Anti-phospholipase A2 receptor antibodies in membranous nephropathy

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Membranous nephropathy (MN) is the most common cause of the nephrotic syndrome in non-diabetic adults. The term MN implies the primary histological change noted on light microscopy, thickening of the glomerular basement membrane (GBM) with little or no cellular proliferation or infiltration. On electron microscopy, dense deposits found in the subepithelial space may be suggestive of circulating antibodies that can permeate the GBM [1]. The antibodies were presumed to be against an antigen, either native or planted, present in the podocyte. From the late 1950s, when Heymann described a rat model of MN, the identification of the target antigens has been a big challenge for nephrologists. Half a century later, in 2009, Beck et al [2] found the circulating phospholipase A2 receptor (PLA2R) antibodies in serum from the patients with idiopathic MN.

Tests for the presence of the PLA2R antigen in kidney biopsy specimens and anti-PLA2R antibodies in serum have improved differential diagnoses and therapy monitoring for patients with MN. The individualized serology-based approach is also possible for the patients with nephrotic syndrome, because anti-PLA2R1 indicates immunologic disease activity and predicts the clinical outcome of idiopathic MN [3,4].

In the PLA2R era, the diagnostic and prognostic values of PLA2R antibodies should be assessed by accurate and sufficient clinical data. In this issue of *Kidney Research and Clinical Practice*, Song et al [5] investigated the prevalence of PLA2R antibodies in Korean patients with MN and suggested that the detection of PLA2R antibodies at the time of diagnosis can predict prognoses and guide treatment decisions in idiopathic MN. Consistent with the previous study that reported the clinical significance of PLA2R antibodies in Korean patients with MN [6], this study showed that PLA2R antibodies were associated with disease activity and clinical outcome, although the number of patients was relatively small. However, some of the results of this study have important implications for future clinical applications of PLA2R, in terms of diagnostic and prognostic values.

The prevalence of PLA2R antibodies showed a large variability among published studies [3–6]. Although the different ethnic origins of the study populations may be responsible, the most influential contributor to the observed discrepancy would be the timing of measurement in relation to the disease course [3,4]. Although the same enzyme-linked immunosorbent assay method was used, the prevalence of PLA2R antibodies was lower in East Asian patients with idiopathic MN (44–54%) than in Western patients [3–6].

At first, the specificity of PLA2R antibodies for idiopathic MN was reported to be approximately 100% [2]. In this study, however, anti-PLA2R antibodies were also detected in 27.8% of patients with secondary MN [5]. Other studies also reported a number of cases of secondary MN that had positive PLA2R antibodies [7,8]. Thus, PLA2R antibodies are not as accurate as previously expected

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in the differential diagnosis of primary and secondary MN, and invasive renal biopsy may be inevitable even in PLA2R antibody-positive patients.

The immunostaining pattern of PLA2R antigens in biopsy specimens can be used as an ancillary diagnostic. In normal kidneys or other glomerular diseases, the PLA2R immunostaining appears only as a weak linear pattern along podocytes. In contrast, strong granular immunostaining is detected in idiopathic MN [4,8].

The identification of PLA2R antibodies has made a significant contribution to the treatment and prediction of prognoses in MN patients. Previous studies have reported that PLA2R antibodies were helpful in predicting the natural course of MN and the response to immunosuppressive therapies [3,4,6]. Song et al [5] also suggested that the risk of progression to chronic kidney disease stage 3 or higher was significantly increased in anti-PLA2R-positive patients compared with anti-PLA2R-negative patients. Taken together, serum PLA2R antibodies should be a valuable prognostic marker for guiding treatment decisions in patients with primary MN. However, it is notable that only half of Korean patients with idiopathic MN are positive for PLA2R antibodies, and there are limitations in establishing the patient treatment strategy based on this antibody level alone.

It is necessary to develop a more sensitive and specific testing method for the detection of PLA2R antibodies. As is evident from the example of thrombospondin type-1 domain-containing 7A [9], the identification of the causative antigens of idiopathic MN other than PLA2R, and commercial diagnostic tests for them, are also urgent. Above all, appropriate clinical studies are needed to ensure that these new autoantibodies are useful to clinical practices as a guide for the diagnosis and treatment of MN.

Conflicts of interest

The author has no conflicts of interest to declare.

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