Immunoglobulin M nephropathy: requiring more attention

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Immunoglobulin M (IgM) nephropathy (IgMN) is a clinicopathological entity initially described in 1978. In early reports, it was mainly described as a disease in which IgM is deposited in the glomerular mesangium in patients with nephrotic syndrome. Since then, related studies have continuously been published, yet it remains a contentious entity. The main controversy begins with whether IgMN should be considered a distinct clinicopathologic entity. Some have classified IgMN as a distinct disease entity and have investigated the clinical and pathological characteristics of IgMN. However, others do not consider it a separate disease entity; instead, they regard it as part of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), with some viewing it as a transitional stage from MCD to FSGS.

Why is there controversy over whether IgMN is an independent entity? When renal pathologists interpret an immunofluorescence (IF) test, glomerular mesangial IgM deposition is often observed in a wide variety of glomerular diseases. In particular, it is well known that weak mesangial IgM staining is not uncommon even in MCD or FSGS where no immune complex deposition is observed. Even in protocol biopsy of transplanted kidneys where no special abnormalities are observed, weak mesangial IgM staining is rarely observed. These observations raise suspicions about whether mesangial IgM deposition may be a nonspecific phenomenon. If IgM deposition is likely to be a nonspecific phenomenon, how can we diagnose IgMN?

For example, a renal pathologist can diagnose MCD when a renal biopsy from a patient with clinically typical idiopathic nephrotic syndrome shows normal light microscopic (LM) findings with no specific glomerular deposits of immunoglobulins or complements in the IF test. Should the presence of weak IgM staining in the mesangium during the IF test warrant a diagnosis of IgMN, or would a diagnosis of MCD with nonspecific IgM deposition be more appropriate? Should a diagnosis of IgMN be considered if the IF test exhibits weak IgM staining in the mesangium? Some will diagnose it as IgMN and others who do not accept IgMN as a separate entity will diagnose it as MCD.

To avoid confusion, precise diagnostic criteria for IgMN are essential. The pathological definition of IgMN is notably clear and intuitive at a glance. IgMN can be defined as diffuse and global predominant mesangial IgM staining on the IF test (Fig. 1). Although these diagnostic criteria seem straightforward, several challenges persist. How intense should IgM staining be? Is it necessary to include the presence of electron-dense deposits (EDD) observed via electron microscopy (EM) within the diagnostic criteria? Furthermore, should the diagnosis of IgMN be independent of clinical manifestations, or should it be confined to patients presenting with nephrotic syndrome, similar to MCD? Should IgMN be restricted to cases showing MCD pattern...
or only mesangial proliferation? Or should the diagnosis of IgMN be determined solely based on IgM deposition, irrespective of LM findings? Definitive diagnostic criteria for IgMN have not yet been established, and various criteria have been applied.

Some renal pathology textbooks mention that IgMN is a variant of MCD and that IgMN should be diagnosed when IgM staining intensity is 2+ or greater among MCD cases, or additionally, EDD should be observed in EM. Since IgMN was first described, many studies have reported on its clinicopathological features, but each study has employed different diagnostic criteria for IgMN. Some studies have classified IgMN as a variant of MCD, and other studies have included FSGS pattern in IgMN. The criteria of IgM staining intensity also vary among studies. In some studies, IgM staining intensity is defined as 2+ or greater [1], while in other studies, it is defined as more than trace [2,3]. Additionally, EDD was included as a criterion in some studies [2]. In several studies, IgMN is classified based solely on IgM deposition, disregarding clinical symptoms or LM findings. In this case, IgMN encompasses a wide array of cases exhibiting diverse clinical presentations, including nephrotic syndrome, non-nephrotic proteinuria, and hematuria, as well as a range of LM findings, such as minimal changes, mesangial proliferation, and FSGS.

The reported prevalence of IgMN during renal biopsy varies significantly, ranging from 1.8% [2] to 11.7% [4], and is reported to be as high as 18.5% in patients with nephrotic syndrome [1]. Meanwhile, studies in Korea reported a prevalence of 4% to 5% [3,5]. The different diagnostic criteria may partly contribute to the wide range of reported prevalences.

For IgMN to be recognized as an independent disease entity, it must first demonstrate clear clinical characteristics that differentiate it from other diseases. In this regard, insights have been gained from several studies that limited their subjects to cases of MCD and investigated differences based on the presence or absence of IgM deposition. Some studies have reported that when MCD was categorized by the presence or absence of IgM deposition, there were no clinical differences attributed to IgM presence [6]. Chae et al. [3] classified IgMN based on IgM deposition and compared cases by dividing them into MCD-like, FSGS-like, and mesangial proliferative glomerulonephritis (MsP-GN)-like IgMN according to light microscopy findings. They found clinical differences among these three categories, including renal function. However, it was also reported that there was no significant difference in the prognosis among the three categories compared to IgM-negative MCD, FSGS, and MsPGN, respectively. These results suggest that IgM deposition may not hold significant clinical importance, supporting the view that IgMN does not suffi-
ciently qualify as an independent entity. However, other studies focusing on MCD have reported that IgM deposition is linked to poor treatment response, early recurrence, or a tendency to progress to FSGS upon rebiopsy [7]. Additionally, Strassheim et al. [8] demonstrated that IgM activates the complement system within the glomeruli, contributing to glomerular damage in an animal study. Zhang et al. [9] have indicated that cases of FSGS with observed IgM deposition exhibit a poorer treatment response and prognosis, suggesting the potential role of IgM in disease progression. These findings provide a clue for considering IgMN as an independent disease entity.

Recurrence of IgMN in transplanted kidneys has been documented several times [10], and I have personally encountered a recurrent IgMN case showing intense mesangial IgM staining in the IF test of allograft kidney. Recurrence of IgMN in transplanted kidneys would also be supporting evidence that IgMN is an independent disease entity.

In this issue of *Kidney Research and Clinical Practice*, Yun et al. [5] compared the clinical characteristics of IgMN with those of other glomerular diseases such as MCD, FSGS, and IgA nephropathy. The authors reported that IgMN exhibited a worse prognosis compared to MCD or IgA nephropathy and demonstrated clinical characteristics more similar to FSGS than to MCD or IgA nephropathy. Furthermore, IgMN displayed pathologic features more akin to FSGS than MCD. In conclusion, the results of this study and some previous studies highlight that IgMN can pose a risk of poor outcomes and poor therapeutic responses, necessitating close attention from both clinicians and renal pathologists.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**Data sharing statement**

The data presented in this study are available from the corresponding author upon reasonable request from the corresponding author.

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**References**