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Editorial

New classification of membranoproliferative glomerulonephritis: a good start but a long way to go

As with other primary glomerulonephritis, pathologic diagnosis of membranoproliferative glomerulonephritis (MPGN) is based on characteristic histologic findings such as mesangial and endocapillary proliferation accompanied by thickening of the glomerular basement membrane (GBM) frequently demonstrating "double contour" due to the interposition of mesangium and infiltration of mononuclear cells into the subendothelial region, deposition of immune complex and/or complement, and the formation of new GBM material.

MPGN has traditionally been classified according to the locations of electron dense deposits, where MPGN I is characterized by mesangial and subendothelial deposits, and MPGN III by the presence of subepithelial deposits in addition to mesangial and subendothelial deposits. Burkholder subtype of MPGN III has prominent subepithelial deposits which correspond to spikes of GBM in light microscopy [1] whereas the Strife and Andes subtype of MPGN III is characterized by subendothelial deposits extending into subepithelial regions across the GBM causing disruption and lamination of lamina densa of GBM [2].

MPGN II, which is diagnosed by very unique electron dense transformations of GBM due to extensive deposition of complement 3 (C3) and other alternative complement pathway (AP) proteins, was considered a separate entity from MPGN mainly because typical microscopic features of MPGN were observed only in a minority of cases and consequently the term was appropriately replaced by "dense deposit disease (DDD)" [3].

Intense staining of the glomerular capillary walls for C3 is the rule in MPGN, and the activation of complement pathways —irrespective of classical or alternative—plays a major role in pathogenesis of MPGN via deposition of complement proteins followed by activation of mesangial and endothelial cells and chemoattraction of leukocytes with resultant damages to capillary walls from released protease and cytokines [4].

One issue related to this important role of complement pathways in MPGN is the question "what causes complement activation in patients with MPGN?" The simultaneous presence of both immunoglobulin (Ig) and complement in immunofluorescence microscopy (IF) suggests that antigen–antibody immune complex (IC) mediates the activation of classical complement pathways (CP). The presence of early complement components such as C1q and C4 in addition to C3 in IF also supports this notion. The diagnostic approach in these patients should include the search for the presence of chronic infections including hepatitis C virus and hepatitis B virus, autoimmune diseases such as SLE, and paraproteinemia due to monoclonal gammopathy, all of which are the major causes of IC formation causing MPGN.

The finding of isolated C3 staining without concomitant Igs in IF together with electron dense deposits in subendothelial and mesangial regions in patients with MPGN was called C3 glomerulonephritis (C3GN) [5], suggestive of the essential role of AP activation in the pathogenesis of glomerular lesions as opposed to Ig-mediated CP activation. C3GN is practically differentiated from DDD by the absence of electron dense transformation of GBM, although both diseases have isolated C3 staining in common. Consequently, diagnostic approaches in DDD and C3GN should focus on genetic or acquired defects inducing uncontrolled activation of AP.

AP, which is constitutively active albeit low grade in the normal state, is tightly regulated by multiple inhibiting proteins. Fluid phase regulators of AP include complement factor H (CFH) and complement factor I (CFI). Complement factor H related proteins (CFHRP) 1–5 have recently been reported to competitively inhibit CFH in a process termed CFH deregulation. Cell bound and surface regulators include decay accelerating factors (DAF: CD55), membrane cofactor protein (CD46), and complement receptor 1. Vitronectin and clusterin act as fluid phase regulators of terminal complement complex [6].

Genetic defects disturbing AP regulation such as mutations in CFH, CFI,CD46, and CFHRP [7–10] and gain of function mutations in factor B and C3 [11] have been observed in DDD and/or C3GN suggesting AP activation as a main pathogenic mechanism in both DDD and GNC3. Moreover, acquired autoantibody C3 convertase, namely nephritic factor (C3NF), which prolongs the half-life of C3 convertase from a few seconds to 60 minutes by preventing the inhibitory action of CFH and stabilizing C3 convertase, have been found in DDD as well as C3GN [7]. Laser microdissection and mass spectrometry of glomeruli from DDD and C3GN showed the similar proteonomic profile which included the protein of AP and terminal complement pathway [12]. Consequently, DDD and C3GN are now regarded as different entities on the same

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spectrum of AP-mediated glomerular disease, the name of which is coined "C3 glomerulopathy" [13].

In brief, the new classification of MPGN is based on the pathogenesis of glomerular injury rather than the morphologic findings of electron dense deposits in the previous classification. MPGN is newly classified into Ig-mediated MPGN showing Ig and C3 in IF and C3 glomerulopathy with isolated C3 staining without Ig which encompass DDD and C3GN.

In this issue, Woo et al [14], timely reclassified MPGN from three tertiary hospitals in Korea according to the new classification. Of 46 cases of MPGN, only two cases of C3GN (4.3%) were found and no cases of DDD were identified. Of the remaining 44 cases of Ig-medicated MPGN, MPGN I and III constituted 61.4% and 38.6%, respectively. Although low serum C3 levels were found in 28% of patients, the frequency of low serum C3 in C3GN, MPGN I, and MPGN III were not provided. One patient with C3GN progressed to ESRD and the renal survival was not different between MPGN I and III.

These results would stimulate further studies related to MPGN (and consequently C3 glomerulopathy) which is by no means a rare and benign disease. In the Progressive REnal disease and Medical Informatics and gEnomic Research (PREMIER) study, a biopsy registry study sponsored by the Korean Society of Nephrology [15], MPGN accounted for 3.0% of biopsy-confirmed glomerulopathy and nephrotic syndrome was the presenting manifestation in 32.7% of MPGN [14]. Compared with nephrotic minimal change disease, the odd ratio of patient death and progression to ESRD in nephrotic MPGN were 4.0 and 72.6, respectively, in a single center study (unpublished observation).

There are several caveats in the definition of C3 glomerulopathy. Although MPGN is the dominant light microscopic finding in C3 glomerulopathy, predominant mesangial proliferative or endocapillary proliferative features were also observed in DDD and C3GN. In some patients with CFHR5 nephropathy, only mild mesangial proliferation was observed in LM [16]. Thus C3 glomerulopathy incorporates MPGN and other morphological diagnosis rather than to be a type of MPGN. On the contrary, some cases of postinfectious glomerulonephritis showing isolated C3 staining some time points during the clinical course can be mistaken as C3GN but resolution of urinary abnormalities and C3 hypocomplementemia at follow-ups would resolve this confusion. Consequently, the integration of clinical, serological, and pathological findings is needed to reach a correct diagnosis.

The pathological differentiation of C3 glomerulopathy from Ig-mediated GN is not always straightforward because small amounts of Ig could be trapped in sclerotic glomeruli or accumulated in podocytes. The dominance of C3 staining rather than purity of C3 staining without Ig should be diagnostic criteria for not missing the diagnosis of C3 glomerulopathy [17]. The more perplexing finding is that either C3NF or genetic mutation of AP proteins observed in C3 glomerulopathy were also present in typical MPGN I. These findings might suggest that AP dysregulation already present in patients could trigger or exacerbate immune complex-mediated renal injury [7]. In this sense, C3 glomerulopathy can be looked upon as a disease process by uncontrolled activation of AP, resulting in Ig-mediated GN in some cases.

Mutation tests for genes encoding various AP proteins such as CFH, CFHRP, CFB, and C3 and complement serological tests seem to play an important role not only in diagnosis, but also in choosing a specific therapeutic option targeting AP in C3 glomerulopathy. For example, replacement of deficient CHF in patients with loss of function mutation in CFH gene by plasma exchange would be theoretically beneficial. A recent expert meeting recommended measurement of serum C3, C4, C3NF, CFH, paraprotein, and screening for CFHR5 gene mutations in patients with C3 glomerulopathy [18], although the feasibility of tests, standardization of measurement methods, and interpretation of test results in a given patient are barriers to be overcome in the implementation of this recommendation. With expanding roles of complement systems identified in various kidney diseases such as atypical hemolytic uremic syndrome, IgA nephropathy, membranous nephropathy, and even in diabetic kidney disease [19] and growing lists of therapeutic options targeting complement pathways such as monoclonal antibody to C5a [20], soluble CR1 [21], in addition to traditional plasmapheresis, genetic and serological tests for complement proteins should be tested and refined in patients with previously well-defined glomerular disease.

In conclusion, Woo et al [14] made a good start in C3 glomeurlopathy in Korea by reclassifying MPGN according to new classification systems but we have to go a long way to assess the patients accurately in terms of genetic or acquired defects in AP pathway causally related to glomerulopathy and to design an appropriate therapeutic plan in individual patients.

Conflict of interest

The author does not have any conflict of interest.

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