EDITORIAL

C3 glomerulopathy, a new but still evolving entity

S.A.M.E.G. Timmermans, P. van Paassen*

Department of Nephrology and Clinical Immunology, Maastricht University Medical Center, Maastricht, the Netherlands. *Corresponding author: p.vanpaassen@maastrichtuniversity.nl

Ever since the clinical introduction of kidney pathology in the mid-1950s, new entities have been introduced into the spectrum of diverse glomerulopathies. Kidney pathology relies on light, immunofluorescence and electron microscopy. Although classification of glomerulopathies for many years has been based on morphology (i.e., the pattern of injury), we currently diagnose patients according to the cause of injury, as identical "patterns" can be linked to distinct mechanisms and thus, targets for treatment.

C3 glomerulopathy (C3G), for example, has been introduced to detect patients with defects in complement activation as the cause of glomerulonephritis (GN). C3G is a rare disease found in ~ 2% of native kidney biopsies annually in the Netherlands (Limburg Renal Registry, unpublished data). Complement defects can be caused by circulating factors, such as (monoclonal) immunoglobulins and/or rare variants in complement genes encoding proteins that either regulate or activate complement, leading to accumulation of C3 fragments and variable glomerular inflammation.[1] In the past, however, many of these patients have been diagnosed with idiopathic proliferative GN, neglecting the crucial role of complement. At present, various complement therapeutics, some with potential efficacy for C3G, are being investigated, making the correct recognition of C3G relevant.

In this issue of *The Netherlands Journal of Medicine*, Koopman and colleagues provide an overview of diagnosis and treatment of C3G.[2] Patients who fulfill the pathologic criteria for C3G, that is, a proliferative GN with dominant staining for C3, either with subtle or no Igs,[1] should be screened for defects in complement regulation.[3] C3 nephritic factor (C3Nef) and, to a lesser extent, factor H autoantibodies (FHAA) can be found in > 50% of patients, enhancing C3 activation and the accumulation of C3 fragments in glomeruli. Igs that interfere with other factors are emerging, although rare. In addition, rare variants in complement genes can be found in ~ 20% patients and, in particular, among familial cases. The interpretation of the genetics of C3G, however, is complex and more research is needed to gain insight into genotype-phenotype correlations; the Database of Complement Gene Variants (http://www.complement-db.org) provides an excellent overview of our current understanding.

The prognosis of C3G varies from clinical remission to end-stage renal disease in ~ 40% and > 10% of patients, respectively. Koopman and colleagues correctly state that no treatment has been proven effective for C3G,[2] although mycophenolate mofetil may protect against disease progression, particularly among patients with C3Nef and/or FHAA serum reactivity.[4] Immunosuppression should therefore be used in patients with "autoimmunity" or in those with a rapid decline in renal function. C3G, by definition, indicates a complement defect, providing a rationale for complement therapeutics. Eculizumab, a potent C5 inhibitor and, to date, the sole commercially available agent, only showed benefit for patients with C3G presenting with vasculitis-like lesions, that is, crescentic GN, on kidney biopsy.[5] Importantly, C3G is caused by activation of C3 upstream of C5 that is not affected by eculizumab. The benefit for patients with "crescentic" C3G may reflect blockade of C5a (i.e., the activation product of C5 and a potent anaphylatoxin), thereby reducing glomerular inflammation, a mechanism that has been proven effective in the anti-neutrophil cytoplasmic antibodies-associated vasculitides.[6] It appears, however, not to prevent the accumulation of C3 fragments within the glomeruli. New therapeutics that specifically target the process of C3 activation, such as factor D inhibitors, are now being studied in phase II clinical trials (e.g., NCT03369236, NCT03459443).

It is important to note that most of the published C3G cohorts represent a mixture of distinct underlying causes, some of which may be linked to monoclonal Igs and/or masked Igs. The high prevalence of monoclonal Igs (often classified as monoclonal gammopathies of renal significance) in adult C3G and the induction of a favorable renal response upon clone-directed treatment[7] suggests a causal link. Apparently, monoclonal Igs in these cases

enhance C3 activation and thereby progression of C3G. Patients with progressive renal disease may therefore benefit from clone-directed treatment,[7,8] whereas treatment may be postponed among those with low-grade proteinuria and no evidence of progression.[9] At present, diagnostic tests that prove the mechanistic link between the monoclonal Igs and complement dysregulation are needed to better select patients for clone-directed treatment.

Moreover, a small subset of patients with C3G may present with false-negative staining for Igs on frozen tissue sections using routine immunofluorescence microscopy;[10] these so called "masked" Igs also can be found in patients with mixed essential cryoglobulinemia or in isolation with no gammopathy. Positive staining for C4d on kidney biopsy indicates the presence of Igs, favoring immunosuppression. It remains to be proven whether complement therapeutics are effective for the treatment of these specific cases.

Taken together, C3G is an important new entity in the diagnostic field of kidney pathology. Better understanding of its etiology and pathogenesis is needed to develop targeted treatment modalities and improve patient care. Koopman and colleagues illustrate the importance of individualized decisions regarding treatment for patients with C3G.[2] The fast evolution of complement therapeutics is promising and may shift the paradigm of treatment towards the targeted approach that makes so much more sense.

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