The many faces of C3 glomerulopathy

To the Editor: The recent article by Sethi et al.,1 "Membranoproliferative glomerulonephritis and C3 glomerulopathy: resolving the confusion," made me revisit a 12-year-old publication.

In 'Apparent progression of acute glomerulonephritis to dense deposit disease'2 we described an 8-year-old boy with hypocomplementemia and meningococcemia. The first kidney biopsy showed glomeruli with abundant deposits of C3 and scarce deposits of IgG. Typical subepithelial humps were observed ultrastucturally, with only occasional subendothelial and intramembranous deposits. Two years later, a new biopsy was again positive for C3, and intramembranous, electron dense ribbon-like change, typical of dense-deposit disease (DDD), was present along the capillary loops, with only occasional subepithelial humps.

In view of the clinical history of our patient, and the typical findings of DDD in the second biopsy, I suggest that the first biopsy, with its scarce subendothelial deposits and no membranoproliferative pattern, might also represent C3 glomerulopathy, similar to cases described by Fakhouri et al.3 and Servais et al.4 One might propose that our case illustrates that C3 glomerulopathy can present with variable faces in the same patient.


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The Authors Reply: We thank Dr Meleg-Smith for her letter1 in response to our article.2 The case you describe of postinfectious glomerulonephritis following meningococcemia progressing to dense-deposit disease (DDD) is very interesting. We have seen similar cases of postinfectious glomerulonephritis progressing to either C3 glomerulonephritis (C3GN) or DDD.

We believe that such cases truly start off as postinfectious glomerulonephritis, and the infection triggers activation of the alternative pathway of complement. However, due to an underlying defect in the regulating mechanisms of the alternative pathway of complement, such as mutations in or antibodies to the complement regulating proteins, the alternative pathway does not revert back to baseline even after the infection is controlled. The consequence is glomerular deposition of complement factors with development of a proliferative glomerulonephritis. If the alternative pathway is slowly brought under control, one is likely to see a mesangial proliferative glomerulonephritis in a subsequent biopsy; if the alternative pathway is chronically activated, a membranoproliferative glomerulonephritis can result.

Whether the activation of alternative pathway leads to a C3GN or DDD may depend on factors such as the site and severity of dysregulation of the alternative pathway. We have also seen cases of transition from a C3GN to DDD phenotype with some loops showing capillary wall deposits typical of C3GN and other loops showing intramembranous deposits of DDD. Thus, as you rightly point out, there are many faces of dysregulation of the alternative pathway of complement. We need to be aware of the heterogeneity in renal biopsy findings to correctly diagnose and manage patients with alternative pathway abnormalities.


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