C3 Glomerulopathy: Overview on a New Disease Entity

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Abstract
The diagnosis of membranoproliferative glomerulonephritis (MPGN) has recently undergone change from an electron microscopy-based classification scheme to one based largely on immunofluorescence findings. Recent advances in our understanding of the disease pathology of membranoproliferative glomerulonephritis has resulted in its re-classification as complement C3 mediated glomerulopathy (C3G) and immune complex-mediated glomerulonephritis (IC-GN). The new concept is based on its underlying pathogenesis, with a key pathogenetic role for the complement alternative pathway (AP), rather than on histomorphological characteristics. This overview summarizes the current state of knowledge about the C3 glomerulopathy.

[Journal of Histopathology and Cytopathology, 2020 Jan; 4 (1):48-54]

Keywords: C3 glomerulopathy, Dense deposit disease, C3 glomerulonephritis, Membranoproliferative glomerulonephritis

Introduction

C3 glomerulopathy (C3G) is an emerging kidney disease caused by dysregulation of the alternative complement pathway.[1,2,3] The characteristic pathology of this disease is glomerular depositions of dominant C3 with absent or weak immunoglobulins. Therefore, C3G is basically diagnosed by immunofluorescence (IF) and it can reveal various patterns of glomerular injuries by light microscopy(LM).[4,5] Following the recent trend of pathogenesis-based reclassification of glomerular diseases, glomerulonephritis associated with alternative complement dysregulation is collectively referred to as C3G.[6] Because laboratory detection of alternative complement dysregulation is still uncommon in current practice, predominant C3 deposition by IF is an initial finding that suggests C3G. However, glomerular diseases caused by mechanisms other than alternative complement dysregulation may occasionally satisfy "C3-dominant deposition with scanty immunoglobulins" as stated in the current consensus report.[4] Clearly, pathogenesis based classification in glomerular diseases is an important prospect for appropriate therapies, but the entity of C3G still presents dilemmas in diagnostic practice by lack of clear definition and pathogenic basis. We review the current status of C3 glomerulopathy, histological, immunofluorescence findings and treatment

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MPGN and C3 Glomerulopathy

Understanding the limitations of current MPGN classification requires a brief review of complement activation pathways. There are two main pathways of complement activation: the classic pathway, which is activated when IgG or IgM antibodies bind to antigens; and the alternative pathway, which does not require the presence of antibodies and can be auto activated by spontaneous cleavage of C3 to C3b, leading to the formation of C3 convertase. The electron microscopy-based classification can result in overlap between types I and III. Both types have been considered to be immune complex-mediated glomerulonephritis but, observations suggest that some cases of MPGN type I or MPGN type III are mediated by complement, not immune complexes.[7,8,9]

So, the historical classification required modification. It is not based on pathogenesis and there is significant overlapping, which is described earlier. In recent years, there have been great advances in our understanding of the pathogenesis of MPGN, particularly in the area of complement-mediated C3 glomerulopathies, including DDD and C3 glomerulonephritis. [4,10]

It is proposed that MPGN be classified into two major groups: immunoglobulin (Ig)-mediated and complement-mediated (C3G). If immunoglobulins are present on IF studies, the evaluation should include a work-up for infections, autoimmune diseases, and monoclonal gammopathies, including cryoglobulins. It should be kept in mind that Ig-mediated MPGN also is associated with extensive C3 (and C4) deposition along the capillary walls via activation of the classic pathway of complement. On the other hand, if the IF studies show predominantly C3 and are negative or show no significant staining for Igs, an in-depth study of the AP is warranted. Ig-mediated MPGN is more likely to be present in adults whereas complement-mediated MPGN is more likely to be present in children and young adults. It is likely that C3G noted in children and young adults is due to genetic mutations in complement-regulating proteins, whereas it is acquired in adults as a result of development of autoantibodies to complement-regulating proteins. Initial evaluation of AP should include serum MAC levels, an alternative pathway functional assay, and hemolytic complement assays. If the initial screening is positive, it should be followed by genetic analysis for mutations and enzyme-linked immunosorbent assays for the presence of autoantibodies to complement-regulating proteins.[11-14]

The current approach, therefore, distinguishes those forms of MPGN with isolated C3 deposits (including DDD and C3GN) as alternative complement pathway-mediated C3G from those cases of MPGN that are mediated by the classical complement pathway with deposits of Ig and complement.

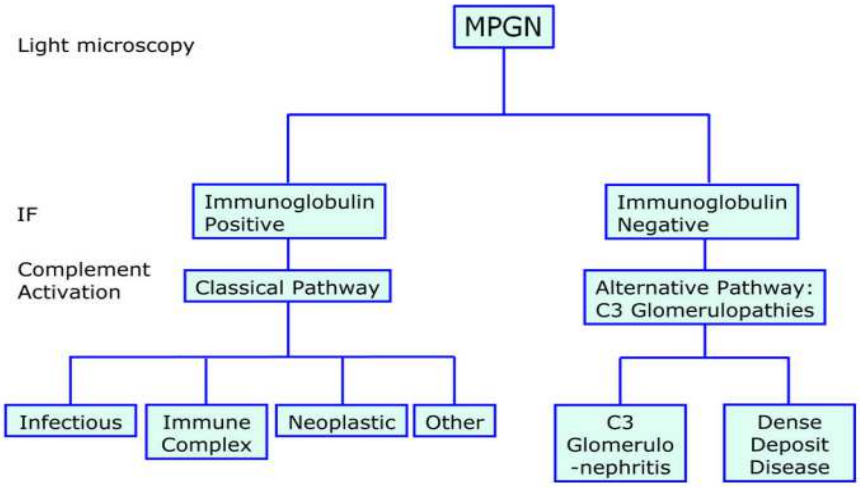

Figure 1. New evolving classification system of membranoproliferative glomerulonephritis.[12,13]

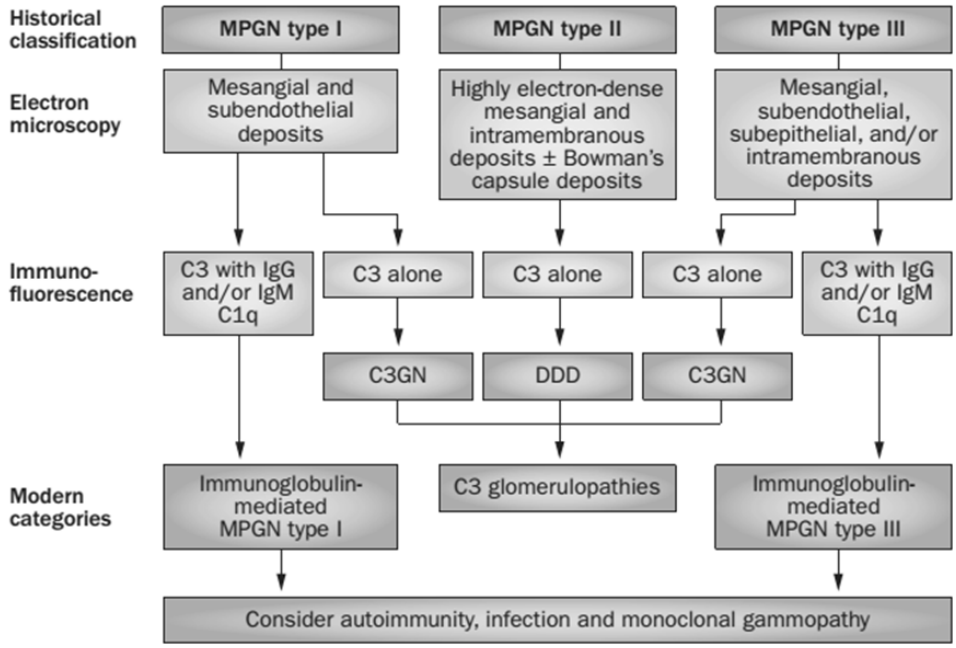

Figure 2. The relationship between historical and modern classification of MPGN[13]

Clinical Presentation

Membranoproliferative glomerulonephritis or C3G are rare diseases with an estimated incidence of 1–2 per million per total population.[15] Patients with C3G present with a variety of symptoms, ranging from a mild disease with asymptomatic microhaematuria and/or proteinuria to a severe disease with nephritic or nephrotic syndrome and renal impairment. Renal survival was worse if the GFR at diagnosis is <60 ml/min/1.73 m2.[16]

The kidney is the major target, possibly due to the morphological specificities of the glomerular capillaries, in particular the fenestrated endothelium, with exposure of the

glomerular basement membrane to serum (complement). Although low levels of C3 are considered a hallmark feature of C3G, in one study low C3 levels were only detected in about 50 % of the patients. Therefore, a normal C3 level does not rule out C3G.[17]

Nasr et al., 2009 studied 32 paediatric and adult patient of dense deposit disease and Lu., et al 2012 studied 92 children and adult patient of dense deposit disease. Both of the studies reveal at presentation, almost all patients have proteinuria usually with haematuria. Nephrotic-range proteinuria is present in two thirds of the patients. Full nephrotic syndrome in 12% to 65% in different series conducted by Lu et al., 2006 and Servais et al., 2012. Persistently, low serum levels of C3 are found in most patients (approximately 80%). Servais et al have reported the clinical features in 56 patients with C3 glomerulopathy without dense deposits (C3GN) and compared them with 29 patients with DDD and 49 patients with immune complex MPGN type 1. The mean age at diagnosis for C3GN was 30, which was significantly higher than for DDD; 25% of patients were below16 years of age. Twenty-seven percent of patients with C3GN had nephrotic syndrome at presentation as compared with 38% of patients with DDD and 65% of patients with MPGN type I.[18,19,20]

Light Microscopy

Light microscopic findings in C3 glomerulopathy can range from membranoproliferative lesions to mesangioproliferative or endocapillary proliferative lesions with or without presence of crescents. In rare instances, light microscopy might be normal. The electron dense osmophilic deposits as seen characteristically in DDD are found within the glomerular basement membrane, and as rounded deposits in the mesangium. In many cases, deposits are also seen in Bowman's capsule and tubular basement membranes. C3 glomerulopathy, in which deposits do not completely fulfill criteria for dense deposits, are classified as C3GN. Electron microscopy in C3GN shows a complex pattern of mesangial increase and glomerular basement membrane thickening. Differing combinations of subendothelial, intramembranous, and subepithelial deposits are noted.[21,22,23]

DDD is defined by the presence of dense osmiophilic transformation of the GBM on EM, and on light microscopy, the morphology is variable. While it is clear that a membranoproliferative pattern of glomerular injury with increased lobulation, mesangial expansion, and capillary wall thickening with segmental double contours is common, a range of other patterns of glomerular involvement also occur. Walker et al., 2007 collected 69 cases of DDD from centers in North America, Europe, and Japan. They identified four distinct histologic patterns on light microscopy: membranoproliferative (25%), mesangial proliferative (45%), crescentic (18%), and acute proliferative and exudative (12%).[21] In the Columbia series conducted by Nasr et al., 2009 which includes 32 cases of DDD, the frequencies were MPGN (44%), mesangial proliferative(28%), endocapillary proliferative (19%), and crescentic GN (9%). These reports emphasize that fewer than 50% of cases of DDD have MPGN morphology. Morphologically, most C3GN cases show either a mesangial proliferative or membranoproliferative pattern.[18]

The dense deposits are recognized on light microscopy by thickening of the GBMs by ribbon-like glassy intramembranous deposits. They stain strongly with eosin and appear somewhat refractile (hyaline). They are intensely periodic acid-Schiff (PAS) positive, and the trichrome stain shows them to be

fuchsinophilic (red) although this reactivity varies among specimens.[23]

Immunofluorescence findings

Immunofluorescence shows characteristic C3 fragment deposition in C3GN.[16] But the deposition of C3 is not always isolated. According to the current consensus report, the term ''isolated'' was replaced by "dominant staining of C3 defined as at least two orders of C3 intensity greater than that of any other immune reactant." [4]

Nasr et al., 2009, Walker et al., 2007, West and McAdams, 1998 studied the immunofluorescence findings. The invariable finding in DDD and C3GN is the presence of C3 in the glomeruli. Intense staining for C3 is noted along the glomerular capillary walls and often in the glomerular mesangial regions. The C3 deposition is usually diffuse and global. The GBM staining may be continuous or discontinuous. The early components of complement, C1q and C4, are usually absent, although occasionally C1q is found. Immunoglobulins are usually absent or show only focal and segmental staining. If they are present, they often stain much less intensely than C3 and they are usually of the IgM type with a segmental distribution; IgG and especially IgA are less common.[18,21,24]

Treatment and Prognosis

Modality of treatment of MPGN is difficult and its prognosis is also guarded. About 50% develop chronic renal failure within 10 years. There is a high incidence of recurrence in transplant recipients, particularly in dense-deposit disease. Treatments with steroids, immunosuppressive agents, and antiplatelet drugs have not been proved to be materially effective.[25]

Eculizumab, the first available anticomplement therapy, blocks at the level of C5 and has revolutionized the treatment of complement-mediated diseases as well as C3 glomerulopathy.[13] This agent is a humanized monoclonal antibody that binds with great affinity to C5 proteins, inhibiting cleaving into C5a and C5b and blocking production of the C5b-9 membrane attack complex. Reports of individual cases showed improvement after treatment, with reduced serum creatinine and proteinuria. Bomback et al 2012, reported that, after 1 year of therapy with eculizumab, there was reduction in active glomerular proliferation and neutrophil infiltration three of five patients, consistent with effective C5 blockade.[26]

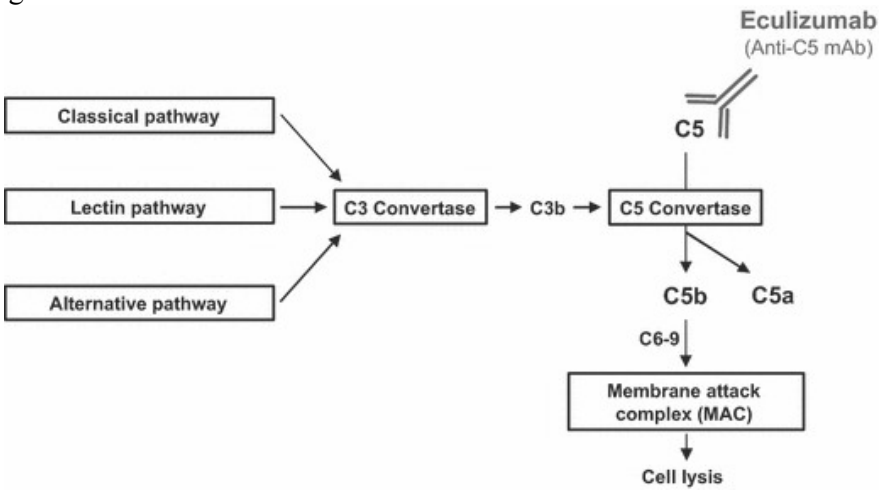

Figure 3. Mechanism of action of eculizumab.[27]

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