21.8.6 Membranoproliferative glomerulonephritis 49

21.8.6 Membranoproliferative glomerulonephritis 4937 Tabitha Turner- Stokes and Mark A. Little

21.8.6 Membranoproliferative glomerulonephritis 4937 Oliveira DB (1997). Poststreptococcal glomerulonephritis: getting to know an old enemy. Clin Exp Immunol, 107, 8–10. Salmon AH, et al. (2004). Recurrence of IgM nephropathy in a renal allograft. Nephrol Dial Transplant, 19, 2650–2. Scolari F, et al. (1990). Familial IgM nephropathy: a morphologic and immunogenetic study of three pedigrees. Am J Nephrol, 10, 261–8. Servais A, et al. (2007). Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uremic syndrome. J Med Genet, 44, 193–9. Walker A, et al. (2007). Eosinophilic glomerulonephritis in children in south western Uganda. Kidney Int, 71, 569–73. Watanabe-Ohnishi R, et al. (1994). Characterization of unique human TCR V beta specificities for a family of streptococcal superantigens represented by rheumatogenic serotypes of M protein. J Immunol, 152, 2066–73.
21.8.6 Membranoproliferative glomerulonephritis Tabitha Turner-Stokes and Mark A. Little ESSENTIALS The key histological features of membranoproliferative glomer- ulonephritis (MPGN) are mesangial hypercellularity, endocapillary proliferation, and capillary wall remodelling. There are two main types: (1) immune complex-mediated disease—caused by chronic infection causing

persistent antigenaemia (notably hepatitis C), autoimmune disease, or monoclonal immunoglobulin produc- tion by plasma cell dyscrasia, and a few ‘idiopathic’ cases; and (2) complement-mediated disease—caused by dysregulation of the alternative pathway of complement, including by C3 neph- ritic factor (C3Nef), an autoantibody that stabilizes the alternative pathway C3 convertase. Clinical presentation is varied, including nephrotic syndrome, episodic visible haematuria, hypertension/rapidly progressive glom- erulonephritis, asymptomatic nonvisible haematuria, and chronic kidney disease. Treatment depends on the underlying disease. All patients should receive appropriate conservative measures (blood pressure control, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker). Underlying infection or monoclonal gammopathy should be treated, when possible, in those with immune complex-mediated MPGN. Eculizumab may have a role in treatment of some patients with complement-mediated MPGN. Steroids and cyclophospha- mide or mycophenolate mofetil are used in patients with severe idiopathic MPGN. Introduction Membranoproliferative glomerulonephritis (MPGN) (synonymous with mesangiocapillary glomerulonephritis) describes a particular histopathological appearance of glomerular inflammation on light microscopy that is common to a heterogeneous group of diseases. The key features are: • mesangial hypercellularity • endocapillary proliferation • capillary wall remodelling through duplication of the basement membrane, which traps immune complexes and cellular elements forming double contours Traditionally, MPGN was classified according to the position of glomerular immune deposits relative to the basement membrane, demonstrated on electron microscopy: • MPGN I: subendothelial deposits • MPGN II: intramembranous electron-dense transformation of the glomerular basement membrane, pathognomonic for dense deposit disease (DDD) • MPGN III: subendothelial and subepithelial deposits However, this classification did not provide much insight into the pathophysiology of the underlying disease causing glomerular in- flammation. A newer classification system divides MPGN into two main types, based on immunofluorescence microscopy: • Immune complex-mediated MPGN—with capillary wall and mesangial deposition of immunoglobulin and C3 on immuno- fluorescence microscopy • Complement-mediated MPGN, termed C3 glomerulonephritis— with capillary wall and mesangial deposition of C3 without immunoglobulin This classification is more practical in the clinical setting as it describes the pathogenetic mechanisms of glomerular inflamma- tion as either immune complex mediated or complement mediated and hence helps guide appropriate further investigations to estab- lish the underlying disease causing MPGN in the individual patient (Fig. 21.8.6.1). Epidemiology MPGN accounts for 7 to 10% of all cases of biopsy-confirmed glom- erulonephritis and is an important cause of endstage renal failure among the primary glomerulonephritides. MPGN occurs in chil- dren and young adults, although patients of any age may be affected, and there is an equal sex distribution. Pathogenesis Immune complex-mediated MPGN Immune complex-mediated MPGN results from circulating im- mune complexes, which are deposited along the glomerular capillary wall, resulting in activation of the classical pathway of complement. This triggers injury in the glomerular capillaries and mesangium, and subsequent recruitment of leucocytes giving rise to the prolif- erative inflammatory glomerular changes seen on light microscopy. Immunoglobulin and complement deposition along the capillary walls can be detected by immunofluorescence microscopy. Circulating immune complexes may be associated with sys- temic autoimmune disease, B-cell dyscrasias (with monoclonal

 immunoglobulin production), or chronic antigenaemia associated with persistent viral, bacterial, or parasitic infection (Table 21.8.6.1). Many of these diseases may be associated with cryoglobulinaemia, which is an important cause

of MPGN. Although systemic lupus erythematosus is arguably the archetypal autoimmune disease associated with immune complex-mediated MPGN, rheumatoid arthritis and Sjögren's syndrome are also common causes. Hepatitis B and C are the most common infectious causes. There is a high incidence of immune complex-mediated glomerulonephritis, particularly MPGN with cryoglobulinaemia, among patients with chronic hepatitis C viral (HCV) infection. Monoclonal gammopathy is an important cause of MPGN in patients who have no evidence of autoimmune disease or chronic infection. Lymphoproliferative malig- nancies may be the source of monoclonal immunoglobulin in some patients, but the most common cause is monoclonal gammopathy of undetermined significance (MGUS), although, in many cases, no circulating monoclonal immunoglobulin can be found. As MPGN- associated MGUS is a significant disease, the term monoclonal gammopathy-associated MPGN or 'monoclonal gammopathy of renal significance (MGRS)' rather than MGUS may be used in these patients. Immunofluorescence studies may point to a specific cause: auto- immune diseases are often associated with deposition of multiple im- munoglobulins along the glomerular capillary wall, including IgG, IgM, IgA, and C1q, along with C3 and kappa and lambda light chains. HCV infection is typically associated with deposition of IgM, IgG, C3, and kappa and lambda light chains. MPGN associated with mono- clonal gammopathy shows kappa or lambda light chain restriction. Complement-mediated MPGN Complement-mediated MPGN results from dysregulation of the alternative pathway (AP) of complement. Complement is an im- portant component of the innate immune system and activation within the glomerular vasculature induces inflammation through chemotaxis of leucocytes and cell lysis, resulting from formation of anaphylatoxins and the membrane attack complex respectively. Immunofluorescence microscopy Immune complex-mediated MPGN C3 glomerulonephritis (C3GN) Chronic infection TMA Complement-mediated MPGN MPGN pattern of glomerular inflammation on light microscopy Capillary wall +/– mesangial deposition of Ig and C3 Activation of classical complement pathway by circulatiog immune complexes Mesangial, subendothelial +/– subepithelial and intramembranous deposits Mesangial, subendothelial +/– subepithelial and intramembranous deposits Intramembranous electron- dense transformation of GBM Dysregulation of alternative complement pathway Capillary wall +/– mesangial deposition of C3 without Ig No glomerular deposition of Ig or C3 Monoclonal gammopathy Systemic autoimmune disease Dense Deposit Disease (DDD) Underlying disease Electron microscopy Pathophysiology of glomerular inflammation Classification of MPGN Fig. 21.8.6.1 New classification system for MPGN based on immunofluorescence microscopy. C3, complement factor 3; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy. Adapted with permission from Sethi et al. (2012). Kidney International, 81, 434–441. Table 21.8.6.1 Causes of immune complex-mediated MPGN Mechanism of immune complex formation Disease Chronic infection

causing persistent antigenaemia Viral: Hepatitis C (HCV)a Hepatitis B (HBV) with or without cryoglobulinaemia Bacterial: Endocarditis Shunt infection Abscesses Parasitic: Malaria Schistosomiasis Autoimmune disease Systemic lupus erythematosus Rheumatoid arthritis Sjögren's syndrome Mixed cryoglobulinaemia Monoclonal immunoglobulin production by plasma cell dyscrasia Monoclonal gammopathy of undetermined significance (MGUS) Myeloma Lymphoma Chronic lymphocytic leukaemia Type I cryoglobulinaemia Unidentified Primary (idiopathic) MPGNb a The most common cause of immune complex-mediated MPGN in patient populations where there is high prevalence of chronic HCV infection e.g. Japan. b An uncommon cause of MPGN, and made only after the listed secondary causes have been excluded.

21.8.6 Membranoproliferative glomerulonephritis 4939 Activation of the complement system occurs via three path- ways: the classical, lectin, and alternative pathways, which converge at C3 to generate an enzyme complex (C3 convertase). The AP is continuously active at low levels in the circulation through spon- taneous hydrolysis of soluble C3, generating C3b, which binds to complement factor B to generate the AP C3 convertase (C3bBb) (Fig. 21.8.6.2). This amplifies activation of the AP, generating chemo- tactic anaphylatoxins (C3a and C5a) and the membrane attack com- plex (C5b–9). In steady state, activation of this pathway is tightly regulated by multiple complement regulatory proteins, which act at different levels of the AP, to avoid overactivation, inappropriate inflammation, and tissue damage. Important regulatory proteins include factor H (CFH), factor I (CFI), factor H-related proteins 1 to 5 (CFHR1–5), and cell-bound membrane cofactor protein, MCP (CD46). Their sites of action are illustrated in Fig. 21.8.6.2. Dysregulation of the AP of complement can occur through autoanti- bodies or genetic mutations that affect the function of these regulatory proteins. This results in glomerular capillary and mesangial deposition of complement components, triggering glomerular inflammation leading to MPGN. Immunofluorescence in this context demonstrates complement deposition without immunoglobulin, distinguishing complement-mediated from immune complex-mediated MPGN. Our understanding of the mechanisms by which dysregulation of the AP occurs in complement-mediated MPGN has advanced greatly over the past few years. Genetic studies in animal models and a few human families with familial nephropathy have demonstrated common underlying genetic defects (Table 21.8.6.2). Many of these mutations affect proteins that regulate the activity of C3 convertase (e.g. CFH, CFI, and CFHR5), leading to overactivity of the AP. Heterozygous mutations in C3 occur in some patients, generating an abnormal C3 convertase, which is resistant to inactivation by CFH. Finally, autoantibodies to these complement regulatory proteins, and to C3 convertase, can re- sult in AP overactivity. In most cases of complement-mediated MPGN there is no family history. As this disease can develop later in life, it is likely that environmental factors, in addition to underlying defects in complement regulatory proteins, are required to initiate renal injury. The two main types of complement-mediated MPGN are DDD and C3 glomerulonephritis (C3GN). Electron microscopy enables Anaphylatoxins: CFH mutation CFHR5 mutation FHAA C3Nef FBAA CFI, CFH, MCP mutations & autoantibodies CFH CFB CFD C3 C3b C3b C5 C3d CFI (+ CFH & MCP) C3c iC3b C3bBb (C3 convertase) C3bBbC3b (C5 convertase) C5b-9 (MAC) C5b C6-9 Cell lysis C5a C3a Amplification loop + Spontaneous hydrolysis continuous ‘tick-over’ Recruitment and activation of circulating leukocytes to glomerulus Fig. 21.8.6.2 Regulation of the alternative pathway of complement and mechanisms of dysregulation in C3 glomerulonephritis. C3 undergoes continuous hydrolysis in the circulation to form C3b, which interacts with CFB and is cleaved by CFD to form C3bBb (the AP C3 convertase). C3bBb cleaves C3 into C3b, which either combines with CFB to create additional C3bBb in an amplification loop or combines with C3bBb itself, generating the C5 convertase enzyme complex, C3bBbC3b. C5 convertase cleaves C5 into C5a and C5b, the latter of which triggers formation of the MAC through activation of complement factors 6 to 9 (C6–9), resulting in cell lysis. C3a and C5a generated by the C3 convertase and C5 convertase enzymes respectively are anaphylatoxins which mediate recruitment and activation of circulating leucocytes to the glomerulus, augmenting glomerular inflammation. As the AP is constitutively active in the circulation, a number of complement regulatory proteins (purple boxes) exist to maintain tight control over activation of this pathway. Autoantibodies to, or genetic mutations affecting the function of these regulatory proteins (green boxes), lead to overactivation of the alternative pathway of complement and glomerular inflammation, resulting in C3 glomerulonephritis. AP, alternative pathway; CFB, complement factor B; CFD, complement factor D; CFH, complement

factor H; CFHR5, complement factor H-related protein 5; CFI, complement factor I; C3Nef, C3 nephritic factor; FBAA, factor B autoantibodies; FHAA, factor H autoantibodies; iC3b, inactivated C3b; MAC, membrane attack complex; MCP, membrane cofactor protein.

section 21 Disorders of the kidney and urinary tract 4940 differentiation between these two diseases: DDD results in a char- acteristic intramembranous electron-dense transformation of the glomerular basement membrane, whereas C3GN is associated with deposits in the mesangial, subendothelial, subepithelial, and/ or intramembranous locations (Fig. 21.8.6.3). Most patients with DDD are positive for C3 nephritic factor (C3Nef), an autoantibody that stabilizes the AP C3 convertase (C3bBb), rendering it resistant to degradation by factor H. However, C3Nef has also been found in a significant proportion of patients with C3GN and so is not a specific marker for DDD. All patients with a detectable C3Nef have marked C3 hypocomplementemia. The differences in the AP dysregulation that lead to divergent patterns of glomerular injury in DDD and C3GN are not understood. A rare variant associated with depos- ition of C4 rather than C3 due to over-activity of the lectin binding pathway (C4 glomerulonephritis) has recently been described. Both DDD and C3GN are encompassed by the term C3 glom- erulonephritis, which describes glomerular inflammation associated with dysregulation of the AP of complement. This term also applies to non-MPGN glomerular pathologies including mesangioproliferative, endocapillary proliferative, and crescentic glomerulonephritis. C3 glomerulonephritis therefore encompasses a spectrum of disease that is dependent on the level and degree of dysregulation of the AP. Patients with DDD may have associated partial lipodystrophy and/or retinal deposits within Bruch's membrane that have a histo-pathological appearance very similar to the glomerular basement membrane deposits. Partial lipodystrophy is thought to result from the deposition of activated complement components in adi-pose tissues, leading to the destruction of adipocytes and loss of subcutaneous fat. MPGN without immune complexes or complement When an MPGN pattern of glomerular inflammation occurs in the absence of immunoglobulin and complement deposition along the Table 21.8.6.2 Genetic and acquired abnormalities associated with dysregulation of the alternative pathway in complement-mediated MPGN Category Target molecule Relative frequency Mutations in complement regulatory proteins Factor H Factor I CFHR5 (CFHR5 nephropathy) MCP (CD46) Most common genetic abnormality Less common than CFH mutation Endemic in Cyprus Uncommon Mutations in complement proteins C3 Reported in familial DDD Autoantibodies to complement regulatory proteins Factor H Factor I Factor B Isolated cases Autoantibodies to complement proteins Alternative pathway C3 convertase—C3bBb (C3Nef) Most common acquired abnormality More common in DDD but also found in C3GN May be associated with CFH and CFI mutations DDD, dense deposit disease; C3Nef, C3 nephritic factor; CFH, complement factor H; CFHR5, complement factor H-related protein 5; CFI, complement factor I; C3GN, C3 glomerulonephritis; MCP, membrane cofactor protein. (a) (b) (c) Fig. 21.8.6.3 Appearance of MPGN on electron microscopy. (a) A case of dense deposit disease illustrating a glomerular capillary loop with electron-dense transformation of the basement membrane (arrows). (b) A case of immune complex-mediated MPGN illustrating a capillary loop with subendothelial (*) and subepithelial (^) electron dense deposits. A new layer of subendothelial basement membrane is formed (arrows), which traps immune deposits and cellular elements between the two layers of basement membrane, forming double contours. (c) A case of thrombotic microangiopathy illustrating a capillary loop with flocculent material (*) trapped between two layers of basement membrane (arrows), containing cellular debris but no electron-dense deposits. Images kindly provided by Professor Terry Cook, Imperial College Renal and Transplant Centre, Hammersmith Hospital, London.

21.8.6 Membranoproliferative glomerulonephritis 4941 capillary wall or mesangium, thrombotic microangiopathy is the most likely diagnosis (Fig. 21.8.6.3). There are multiple possible aetiologies of thrombotic microangiopathy, but all share in common endothelial injury, which triggers acute inflammation in glomerular capillaries. Clinical features The clinical presentation of MPGN is varied, reflecting the hetero- geneity in the underlying diseases causing this pattern of glomerular inflammation. The proliferative pattern of glomerular inflammation and re- modelling of the glomerular basement membrane gives rise to an active urinary sediment with nonvisible haematuria and significant proteinuria, which is often in the nephrotic range. Indeed, a mixed 'nephrotic–nephritic' picture is highly suggestive of MPGN. The de- gree of renal impairment varies depending on the underlying dis- ease and severity of glomerular inflammation and scarring. Patients may present with: • overt nephrotic syndrome • episodic visible haematuria, often associated with upper respira- tory tract infections, similar to IgA nephropathy • severe hypertension and rapidly progressive renal impairment with oliguria ('rapidly progressive glomerulonephritis') • asymptomatic nonvisible haematuria and proteinuria detected on routine screening • advanced renal impairment with or without symptomatic uraemia Patients with DDD may have associated partial lipodystrophy affecting the face, upper limbs, and torso (Fig. 21.8.6.4). Additionally, fundoscopy may reveal drusen (yellow or white de- posits) between the basement membrane of the retinal pigment epithelium and Bruch's membrane. This may be associated with macular degeneration and the long-term risk of visual loss is approximately 10%. Most patients develop progressive renal impairment, although the time to progression to endstage renal failure is variable. Those that have severe renal impairment at diagnosis, heavy pro- teinuria, or extensive scarring on renal biopsy tend to progress more rapidly. DDD carries the greatest overall risk of developing endstage renal failure. Recurrence after renal transplantation is common.
Clinical investigations The diagnosis of MPGN is made following renal biopsy showing the characteristic features on light microscopy described earlier. The presence of immunoglobulin and complement on immunofluorescence microscopy should prompt investiga- tion for underlying systemic autoimmune disease, monoclonal gammopathy, cryoglobulinaemia, and chronic infections, par- ticularly HCV. The presence of complement without immunoglobulin on im- munofluorescence microscopy should prompt further investigation of the AP. Serological complement assays are useful in investigating uncontrolled activation of the AP, which is suggested by low serum C3, normal C4, and often reduced factor B levels. Increased C3 turnover can be demonstrated by increased serum levels of C3 breakdown products (e.g. C3c and C3d), in association with low C3. Similarly, low serum C5 with increased soluble C5a and C5b– 9 (soluble membrane attack complex) levels suggest increased C5 turnover. Haemolytic assays of complement activity for the clas- sical (CH50) and alternative (AH50) pathways should also be used to identify dysregulation of AP activity. Other recommended com- plement investigations assess for autoantibodies to, or genetic mu- tations affecting, complement-regulating proteins that lead to AP dysregulation (Table 21.8.6.3). Many of these tests require referral to specialist centres. Treatment Treatment of MPGN varies by underlying disease. Most studies of MPGN treatment were conducted before the role of dysregulation of the AP of complement was appreciated, hence this evidence base is of limited use in modern clinical practice. All patients should receive appropriate conservative therapy with antiproteinuric agents (angiotensin-converting enzyme in- hibitor therapy or angiotensin II receptor blockade) to minimize proteinuria, and antihypertensives to achieve strict blood pressure control, aiming for target blood pressures established for patients with CKD. Immune complex-mediated MPGN Patients with underlying systemic autoimmune connective tissue disease should be treated with appropriate immunosuppression Fig. 21.8.6.4

Facial appearance in partial lipodystrophy. This patient has had silicone pads inserted into her cheeks, accounting for the bulges in the regions where adipose tissue has been completely lost.

section 21 Disorders of the kidney and urinary tract 4942 according to the underlying disease, preferably in an appropriate specialist setting. MPGN associated with chronic infection requires appropriate treatment of the underlying infection. Patients with chronic HCV infection associated with cryoglobulinaemia that develop rap- idly progressive renal failure or systemic vasculitis may require treatment with immunosuppressive agents (including cortico- steroids, rituximab, or cyclophosphamide) and plasma exchange, in addition to antiviral therapy. However, antiviral therapy is the mainstay of treatment and the 2018 KDIGO Clinical Practice Guidelines recommend treatment with directly acting anti-viral agents (such as Grazopevir or elbasavir). Ribavarin should be avoided if GFR < 30ml/min per 1.73m2. Appropriate antiviral therapy in patients with HCV-associated MPGN is changing sig- nificantly and will continue to do so—it should be guided by a hepatologist. Evidence of an associated monoclonal gammopathy should prompt referral to a haematologist to establish the nature of the underlying plasma cell dyscrasia and initiate appropriate chemo- therapy. There is limited evidence to guide treatment for MGUS- associated MPGN but, as these patients are likely to have an unidentified plasma cell dyscrasia, they may benefit from myeloma- targeted treatment regimens and/or rituximab. Complement-mediated MPGN Treatment of complement-mediated MPGN would logically depend on the mechanism of complement dysregulation, although no cur- rent treatments are of proven benefit. Patients with CFH deficiency may benefit from periodic plasma infusion, and purified or recom-binant factor H preparations are likely to be available in the future. Those with autoantibodies against complement factors or regulatory proteins may benefit from plasma exchange and immunosuppres- sive therapy. The development of eculizumab, and the evidence for its efficacy in atypical haemolytic syndrome associated with AP dysregulation, provides a possible new treatment option for complement-mediated MPGN. A monoclonal antibody against C5, it inhibits its cleavage by C5 convertase, preventing generation of the terminal complement complex C5b–9. The role for eculizumab in treating complement- mediated MPGN associated with different mechanisms of AP dysregulation requires further study. However, it may be a new and effective treatment in some forms, particularly in those patients who have evidence of C5 activation in the plasma (e.g. increased levels of soluble C5b–9) or kidney (e.g. increased glomerular C5b–9 depos- ition on immunofluorescence microscopy). Idiopathic MPGN Following recent advances in understanding the pathogen- esis of MPGN, idiopathic MPGN is now considered uncommon and should be a diagnosis of exclusion, made only following thorough investigation for all possible secondary causes listed in Table 21.8.6.2. The KDIGO Clinical Practice Guidelines on the management of idiopathic MPGN (2012) recommend cyclophos- phamide or mycophenolate mofetil plus corticosteroid therapy only for patients with rapidly progressive renal impairment, se- vere nephrotic syndrome, or crescent formation on renal biopsy. Conservative therapy alone is recommended for patients with mild disease. However, the overall evidence for the efficacy and safety of this treatment regimen is weak. Recurrence after renal transplantation Recurrence of MPGN occurs in 27 to 65% of cases following renal transplantation. Low complement levels may be an early marker for recurrence. Early recurrence, and a more aggressive disease course, is commonly associated with an underlying monoclonal gammopathy. DDD almost universally recurs in renal transplants, with a 5-year allograft failure rate of 50%. FURTHER READING Bomback AS, Appel GB (2012). Pathogenesis of the C3 glomerulopathies and reclassification of MPGN. Nat Rev Nephrol, 8, 634–42. Bomback AS, et al. (2012). Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol, 7, 748–56. Table 21.8.6.3 Recommended investigations

to determine aetiology of MPGN Immune complex-mediated MPGN Autoimmune disease Clinical evaluation for evidence of systemic connective tissue disease Autoantibodies associated with systemic lupus erythematosus, Sjögren’s syndrome, and rheumatoid arthritis Chronic infection Serology and polymerase chain reaction for HCV and HBV infection Blood cultures Cardiac echocardiogram (bacterial endocarditis) Cryoglobulins in patients with chronic HCV infection Monoclonal gammopathy Serum and urine protein electrophoresis Immunofixation studies Serum free light chains ± Bone marrow investigations Complement-mediated MPGN Screening tests recommended in all patients Serum C3 and C4 levels Serum factor H level C3 nephritic factor (autoantibody against C3 convertase, C3bBb) Screening for CFHR5 mutation Specialist tests considered on case-by-case basis Serum factor B level Serum C5 level Measurement of markers of C3 activation (e.g. C3d, C3c) Measurement of markers of C5 activation (e.g. soluble C5b–9) Anti-factor H autoantibodies Anti-factor B autoantibodies Mutation screening of complement regulatory proteins (CFH, CFI, CD46), activation protein genes (C3, CFB), and assessment of copy number variation across the CFH–CFHR locus. Recommended complement investigations from Pickering et al. (2013). C3 glomerulopathy: a consensus report. Kidney Int, 84, 1079–89.

Revision #1
Created 2026-01-22 16:41:40 UTC by Omar Ayman
Updated 2026-01-22 16:41:40 UTC by Omar Ayman