C3 Glomerulonephritis: From Diagnosis to Management in a Unique Patient Case

Pedro Castro[1*], *Nuno Oliveira*[1], *Rui Alves*[1]
1. Nephrology Service, Hospitais da Universidade de Coimbra, Unidade Local de Saúde de Coimbra, Coimbra, Portugal

https://doi.org/10.71749/pkj.52

Abstract
C3 glomerulopathies (C3G) are ultra-rare diseases driven by dysregulation of the alternative pathway in the complement system, leading to glomerular C3 deposition and inflammation. C3G includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), both associated with progression to end-stage renal disease (ESRD). This report presents a C3GN case, highlighting diagnostic and therapeutic complexities.
A 19-year-old male with recurrent macroscopic hematuria triggered by respiratory infections was initially managed for suspected IgA nephropathy. Follow-up revealed persistent low serum C3 levels, prompting a kidney biopsy that confirmed C3GN with a membranoproliferative pattern and dominant C3 deposits. Genetic testing revealed a C3 mutation and positive anti-Factor H antibodies. Despite treatment with renin-angiotensin-aldosterone system blockade, steroids, and mycophenolate mofetil (MMF), the patient's proteinuria fluctuated, requiring adjustments in immunosuppressive therapy.
C3GN can mimic other glomerulonephritides such as IgA nephropathy and atypical hemolytic uremic syndrome (aHUS). Accurate diagnosis relies on kidney biopsy findings and complement studies; genetic testing can provide critical insights. While available therapies, including immunosuppressants and complement inhibitors, offer partial benefit, C3GN often progresses, underscoring the need for novel, more effective treatments.
This case illustrates the diagnostic challenges of C3GN in patients with hypocomplementemia and recurrent hematuria. It emphasizes the importance of targeted research into complement therapies to potentially improve outcomes for C3G.

Keywords: Complement C3; Glomerulonephritis; Glomerulonephritis, Membranoproliferative

INTRODUCTION
C3 glomerulopathies (C3G) are a newly recognized group of ultra-rare diseases arising from primary abnormalities in the alternative pathway of the complement system.[1] In C3G, complement dysregulation occurs in the fluid phase rather than on the endothelial surface, leading to C3 fragments circulating and depositing in the kidney, which promotes glomerular inflammation.[2] This pathophysiology contrasts with that of primary complement-mediated atypical hemolytic uremic syndrome (aHUS), in which alternative pathway dysregulation occurs on endothelial surfaces, resulting in C5b-9 formation, endothelial injury, and associated thrombotic microangiopathy symptoms.[2,3] Clinical signs and symptoms of C3G resemble those of other primary glomerulonephritides: most patients present with varying degrees of proteinuria and hematuria, ranging from asymptomatic cases detected during routine checks to presentations of nephrotic syndrome. Hypertension is common either at presentation or during follow-up, as is a reduced glomerular filtration rate.[4] Although reduced serum C3 levels are observed in up to 75% of C3G patients, this finding is not exclusive and may also occur in aHUS and post-infectious glomerulonephritis, thus requiring a kidney biopsy for an accurate diagnosis.[3] The pathological hallmark of C3G is isolated or dominant glomerular C3 deposits on immunofluorescence, with common histological patterns such as membranoproliferative glomerulonephritis (MPGN).[1,3] Electron microscopy further differentiates dense deposit disease (DDD) from C3 glomerulonephritis (C3GN) based on the electron-dense complement deposit pattern.[1,3] Up to 50% of C3G patients progress to end-stage kidney disease within 10 years, despite various treatment approaches—including RAAS blockade, steroids, mycophenolate mofetil (MMF), rituximab, and complement inhibitors—demonstrating varying degrees of efficacy.[5-11] Here, we present a case of C3GN, emphasizing the diagnostic and treatment challenges of this rare disease and the importance of clinical trials in evaluating new therapies that may shift treatment paradigms.

Received: 05/11/2024 **Accepted:** 30/01/2025 **Published Online:** 06/02/2025 **Published:** 16/05/2025
* **Corresponding Author:** Pedro Castro | pedro.aam.castro@gmail.com | ULS Coimbra, Praceta Professor Mota Pinto, 3004-561 Coimbra
© Author(s) (or their employer(s)) and PKJ 2025. Re-use permitted under CC BY 4.0. (https://creativecommons.org/licenses/by/4.0/)

CASE REPORT

Initial History

We present the case of a 19-year-old male with a long-standing history of recurring macroscopic hematuria following acute upper respiratory infections. He had been followed in the Pediatric Nephrology clinic at Coimbra's Pediatric Hospital since 2001, around age 4, with a presumptive diagnosis of IgA Nephropathy. His diagnostic workup at that time was extensive and included: negative anti-nuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies, normal anti-streptolysin titer, and an immunoglobulin profile showing elevated IgE. Complement testing revealed very low C3 with normal C4, interpreted as possibly related to a congenital deficiency. No kidney biopsy was performed, and a presumptive diagnosis of IgA Nephropathy was established.

Medical records from this period indicate a single episode of acute asthma, along with an allergy workup that showed positive Phadiatop to pollen and dust mites. He had no family history of kidney disease, and both siblings appeared healthy.

During follow-up in his pediatric years, he was treated with enalapril. His kidney function remained normal, with proteinuria under 1 g/24 hours.

Diagnosis

The patient was referred to adult Nephrology for follow-up in March 2014. At that time, he reported repeated episodes of macroscopic hematuria, but no other clinical symptoms. He had good blood pressure control, no peripheral edema, and normal serum creatinine, although proteinuria had worsened to over 1 g/24 hours. A diagnostic workup was repeated, showing persistently low C3 and CH50 levels with normal C4; all other studies were negative (Table 1).

Table 1. Initial diagnostic work-up.

Serology	
Anti-dsDNA	NEGATIVE
ANA	NEGATIVE
Anti-MBG	NEGATIVE
ANCA	NEGATIVE
C3 (N: 0.82-1.85 g/L)	<0.11 g/L
C4 (N: 0.15-0.53 g/L)	0.2 g/L
CH50 (N: 41-95 IU/mL)	<13.5 IU/mL
Cryoglobulins	NEGATIVE
Serum electrophoresis	NORMAL
Serum immunofixation	NO MONOCLONAL COMPONENT
FLC kappa (N: 3.1-19.7 mg/L) FLC lambda (N: 5.7-26.3 mg/L) Ratio FLC K/L (N: 0.26-1.65)	17.4 11.2 1.55
Human Immunodeficiency virus	Negative
Hepatitis B virus (HBV)	IMMUNE
Hepatitis C virus (HCV)	NEGATIVE
Biochemistry	
Serum creatinine	1 mg/dL
LDH	127 IU/L
Serum iron	48 ug/dL
Ferritin	176 ng/mL
Erythrocyte Sedimentation Rate	9 mm/h
Hemogram	
Hemoglobin	12.8 mg/dL
Leucocytes	5.6/per mm3
Platelets	85 000/mm3
Urine	
Urinary sediment	10 RBC/HPF <1 Leucocytes/HPF
24 hour proteinuria	2.2 g
Urinary immunofixation	NO MONOCLONAL COMPONENT

FLC: free light chains.

A kidney biopsy was performed in April 2015, revealing a membranoproliferative glomerulonephritis pattern, with two cellular/fibrous crescents and heavy C3 deposition on immunofluorescence (IF) (Figs. 1A and 1B). The diagnosis of C3 Glomerulopathy was confirmed. Additional workup (Table 2) included: genetic testing (next-generation sequencing -NGS and multiplex ligation-dependent probe amplification-MLPA panels for atypical hemolytic uremic syndrome), revealing a heterozygous mutation in C3 not previously described, but with a high probability score of pathogenicity; positive anti-factor H antibodies, measured by enzyme-linked immunosorbent assay (ELISA).

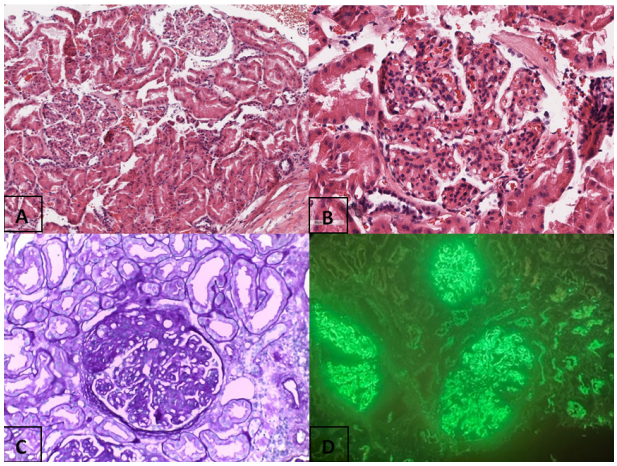


Figure 1. A: The glomeruli show a classic MPGN pattern with lobulation of the capillary wall; the tubules and interstitium show no significant morphologic changes (H&E 40x).
B: Higher amplification of a glomerulus showing endocapillary proliferation and discrete thickening of the capillary walls (H&E 100x); C: Glomerulus with formation of cellular/fibrocellular crescent (PAS, 100x). D: C3 positivity on IF.

Table 2. Additional genetic and immunological testing.

Test	Result
NGS panel for atypical hemolytic uremic syndrome CFH, CD46, CFI, C3, THBD, CFB, CFHR3, CFHR4 e DGKE.	Mutation in C3 factor, not previously described but with a high probability score of pathogenicity score 1.00 (polyphen-2) Ex.8,c.820G>A, p.Gly274Arg- heterozygosity
MLPA CFH, CD46, CFI, CFHR3/CHFR1	Negative
C3 Nephritic factor	Negative
Anti factor H antibodies (N: <27 IU/mL)	36 IU/mL

Treatment and Follow-Up

Initial treatment optimization involved double renin-angiotensin-aldosterone system blockade. Routine immunizations for influenza were administered annually, and an anti-pneumococcal vaccine was given in 2014. Other treatments included intermittent oral iron for anemia and topical nasal steroids for allergic rhinitis.
Fig. 2 presents evaluations and treatment schedules from 2015 to 2022.

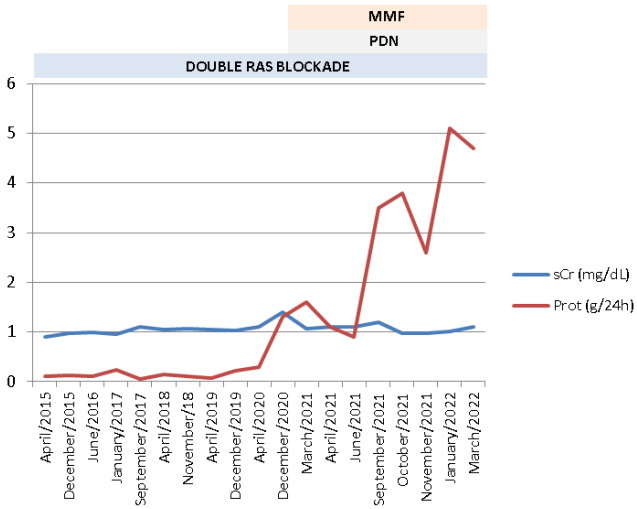


Figure 2. Evolution of proteinuria, serum creatinine and therapy since the first appointment

From the start of follow-up until the end of 2020, the patient maintained stable kidney function, bland urinary sediment, and proteinuria below 300 mg/day. However, in a subsequent evaluation, proteinuria increased markedly, along with microscopic hematuria and a transient increase in baseline serum creatinine. In March 2021, given the progressive proteinuria and signs of microvascular inflammation, we initiated oral prednisolone (1 mg/kg/day for 1 month, tapered to 5 mg/day by six months and 2.5 mg/day thereafter) and MMF (starting at 1 g/day, increased to 3 g/day as tolerated). Despite an initial response, with proteinuria decreasing to 1 g at 3 months, a subsequent deterioration in proteinuria led us to reduce MMF dosage to 2 g/day by March 2022. A kidney biopsy was repeated at this time, which again showed a membranoproliferative glomerulonephritis pattern and abundant C3 deposition on IF. On electron microscopy, these deposits were mainly located on mesangial and sub-endothelial areas and had no characteristics of dense deposit disease, which confirmed the diagnosis of C3 glomerulonephritis.

The patient was then enrolled in a clinical trial with an anti-factor B inhibitor, which is still ongoing.

DISCUSSION

This case of C3 glomerulonephritis (C3GN) highlights both the complexity of diagnosing complement-mediated renal diseases and the challenges in effective long-term management. C3G, an umbrella term encompassing C3GN and dense deposit disease (DDD), is an ultra-rare disease caused by dysregulation of the alternative pathway of the complement system. In contrast to atypical hemolytic uremic syndrome (aHUS), where complement activation occurs on endothelial surfaces, in C3G, the dysregulation is primarily fluid-phase, leading to glomerular deposition of C3 fragments and subsequent inflammatory injury.[9,8]

The case presented here underscores the difficulty of differentiating C3G from other glomerulopathies. Initially diagnosed with IgA nephropathy due to episodic hematuria and a history of upper respiratory infections, our patient exhibited overlapping clinical features, which is not uncommon. Persistent low serum C3 levels and worsening proteinuria raised suspicion for an alternate diagnosis, with biopsy findings ultimately confirming C3GN. Given the wide differential diagnosis and overlap in laboratory findings, kidney biopsy remains crucial for an accurate C3G diagnosis, particularly when complement levels are persistently low and other serologies are non-revealing.[10,11] The presence of a heterozygous C3 mutation and positive anti-factor H antibodies in this patient highlights the genetic and immunologic complexity often associated with C3G. These findings suggest the presence of both genetic and acquired factors in disease pathogenesis. Although C3G is typically a disease of complement dysregulation in the fluid phase, genetic predispositions, such as mutations in complement proteins, may influence clinical severity and treatment responses.[12] Therapeutic options for C3G are limited and largely unproven in their efficacy. Conventional therapies—such as renin-angiotensin-aldosterone system blockade, corticosteroids, and immunosuppressive agents like mycophenolate mofetil—yield variable outcomes. In this case, initial RAAS blockade stabilized renal function for several years, but the patient experienced disease progression with worsening proteinuria and renal impairment.

Evidence for the use of mycophenolate mofetil in C3G, comes from two small number observational studies (enrolling 60 and 30 patients), that showed significant higher rates of remission in the mofetil groups, compared to other immunosuppression options.[5,6]

In our patient, a course of immunosuppressive therapy with corticosteroids and increased doses of mycophenolate mofetil in response to proteinuria yielded only transient improvements, followed by subsequent relapse, suggesting the need for alternative or adjunct therapies.

This outcome highlights the variable response seen in C3G, likely due to the heterogeneous mechanisms underlying complement dysregulation in affected individuals.[13,14] Indeed, further analysis of data from the Spanish group of patients treated with mycophenolate mofetil showed that responders were mostly patients with nephritic factors (8/10), contrasting with the group without nephritic factors (and presumably a genetic basis for the disease), that showed only limited response (3/8).[5] In our patient, the presence of a genetic basis for the disease (a pathogenic C3 variant) could, possibly, account for the lack of response to mycophenolate mofetil.

A course of therapy with the anti-C5 inhibitor eculizumab was considered; however, observational, registry data related to the use of this drug in C3G, revealed that a favourable response with this drug was only found in patients with a rapidly progressive disease and extracapillary proliferation in kidney biopsy samples.[15] These findings may reflect the fact that eculizumab only blockades the terminal complement cascade, with no effect on C3 complement dysregulation that is the main driver of the disease. With these considerations in mind, other options were considered, namely, the enrolment in a clinical trial.

Recent advancements in complement-targeted therapeutics offer promising avenues, such as C5 inhibitors, C3 inhibitors, and factor B inhibitors, which aim to directly modulate the complement pathway abnormalities seen in C3G. However, access to and clinical trials for these newer agents remain limited, especially given the rarity of C3G.[3,16,17] After a review of available options, an enrolment in a trial involving the factor B inhibitor LNP023, was the followed course; this trial was recently completed, and the results should be published in the short term.[18] Factor B is a critical component of the alternate pathway C3 convertase (C3bBb); in C3G animal models, mice with targeted deletion of factor B are incapable of forming the

convertase and of developing the disease phenotype. Thus, a drug inhibiting this factor is a promising option.

In summary, this case exemplifies the ongoing clinical challenges in diagnosing and managing C3G. Comprehensive genetic and immunologic testing may improve diagnostic precision and facilitate individualized therapeutic approaches. As novel complement inhibitors become available, future research should prioritize assessing these agents in controlled trials to determine their efficacy in modifying disease course and improving renal outcomes. The patient's management reinforces the necessity of multidisciplinary care and long-term follow-up in this complex, evolving field of nephrology.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Contributorship Statement

PC and NO: Responsible for the writing of the manuscript.
RA: Responsible for reviewing the manuscript.
All authors approved the final version to be published.

REFERENCES

1. Fakhouri F, Frémeaux-Bacchi V, Noël LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. Nat Rev Nephrol. 2010;6:494-9. doi: 10.1038/nrneph.2010.85.
2. Durey MA, Sinha A, Togarsimalemath SK, Bagga A. Anti-complement-factor H-associated glomerulopathies. Nat Rev Nephrol. 2016;12:563-78. doi: 10.1038/nrneph.2016.99.
3. Goodship TH, Cook HT, Fakhouri F, Fervenza FC, Frémeaux-Bacchi V, Kavanagh D, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017;91:539-51. doi: 10.1016/j.kint.2016.10.005.
4. Feehaly J, Floege, J, Tonelli, M, Johnson, R. Comprehensive Clinical Nephrology. 6th ed. Amsterdam: Elsevier; 2019.
5. Rabasco C, Cavero T, Román E, Rojas-Rivera J, Olea T, Espinosa M, et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. Kidney Int. 2015;88:1153-60. doi: 10.1038/ki.2015.227.
6. Avasare RS, Canetta PA, Bomback AS, Marasa M, Caliskan Y, Ozluk Y, et al. Mycophenolate Mofetil in Combination with Steroids for Treatment of C3 Glomerulopathy: A Case Series. Clin J Am Soc Nephrol. 2018;13:406-13. doi: 10.2215/CJN.09080817.
7. Giaime P, Daniel L, Burtey S. Remission of C3 glomerulopathy with rituximab as only immunosuppressive therapy. Clin Nephrol. 2015;83:57-60. doi: 10.5414/CN107945.
8. Servais A, Frémeaux-Bacchi V, Lequintrec M, Salomon R, Blouin J, Knebelmann B, et al. Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. J Med Genet. 2007;44:193-9. doi: 10.1136/jmg.2006.045328.
9. Pickering MC, D'Agati VD, Nester CM, Smith RJ, Haas M, Appel GB, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013;84:1079-89. doi: 10.1038/ki.2013.377.
10. Bomback AS, Appel GB. Pathogenesis of the C3 glomerulopathies and reclassification of MPGN. Nat Rev Nephrol. 2012;8:634-42. doi: 10.1038/nrneph.2012.213.
11. Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA, Traynor C, Flanagan M, Wong L, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. Clin J Am Soc Nephrol. 2014;9:46-53. doi: 10.2215/CJN.04700513.
12. Martínez-Barricarte R, Heurich M, Valdes-Cañedo F, Vazquez-Martul E, Torreira E, Montes T, et al. Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation. J Clin Invest. 2010;120:3702-12. doi: 10.1172/JCI43343.
13. Zhang Y, Meyer NC, Wang K, Nishimura C, Frees K, Jones M, et al. Causes of alternative pathway dysregulation in dense deposit disease. Clin J Am Soc Nephrol. 2012;7:265-74. doi: 10.2215/CJN.07900811.
14. Smith RJ, Harris CL, Pickering MC. Dense deposit disease. Mol Immunol. 2011;48:1604-10. doi: 10.1016/j.molimm.2011.04.005.
15. Le Quintrec M, Lapeyraque AL, Lionet A, Sellier-Leclerc AL, Delmas Y, Baudouin V, et al. Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy. Am J Kidney Dis. 2018;72:84-92. doi: 10.1053/j.ajkd.2017.11.019.
16. Bomback AS, Smith RJ, Barile GR, Zhang Y, Heher EC, Herlitz L, et al. Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol. 2012;7:748-56. doi: 10.2215/CJN.12901211.
17. Nester CM, Smith RJ. Treatment options for C3 glomerulopathy. Curr Opin Nephrol Hypertens. 2013;22:231-7. doi: 10.1097/MNH.0b013e32835da24c.
18. Wong E, Nester C, Cavero T, Karras A, Le Quintrec M, Lightstone L, et al. Efficacy and Safety of Iptacopan in Patients With C3 Glomerulopathy. Kidney Int Rep. 2023;8:2754-64. doi: 10.1016/j.ekir.2023.09.017.