C3 glomerulonephritis in Colombia

The response to prednisone and mycophenolate mofetil in a clinical case

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Abstract

Introduction: C3 glomerulonephritis is a recent condition that consists of dysregulation of the alternative complement pathway, with subsequent hyperactivation and glomerular C3 deposits. Patients may present hematuria and proteinuria, nephrotic syndrome and, less often, acute kidney injury or rapidly progressive glomerulonephritis. Treatment is still unclear and is based mainly on international reports and series.

Case presentation: we present the case of a young adult with nephrotic syndrome secondary to C3 glomerulonephritis who was treated with prednisone and mycophenolate mofetil with a partial clinical and biochemical response.

Conclusion: C3 glomerulonephritis is a rare condition with no clearly established treatment options thus far, as shown in the presented case. **(Acta Med Colomb 2026; 51. DOI: https://doi.org/10.36104/amc.2026.4830).**

Keywords (DeCS): *C3 glomerulonephritis, nephrotic syndrome; membranoproliferative glomerulonephritis, prednisone, mycophenolate mofetil.*

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Introduction

Complement 3 glomerulonephritis (C3GN) is a rare form of glomerulonephritis that affects both children and adults, caused by complement alternative pathway dysregulation and classified as a C3 glomerulopathy (1, 2). Its clinical presentation varies, and diagnosis is based on kidney biopsy immunofluorescence.

Studies in the international literature have explored treatment options like steroids, mycophenolate mofetil, and complement inhibitors. However, reports in Colombia and Latin America have been limited to a clinical and histological description, specifically regarding the use of eculizumab, without detailing the response to prednisone and mycophenolate mofetil.

In this report, we describe the case of a young adult with C3GN treated with prednisone and mycophenolate mofetil, highlighting the importance of producing local evidence regarding the therapeutic response of this group of patients.

Case presentation

A male patient in his 20s consulted due to a six-month history of lower extremity edema and low-back pain. Laboratory tests on admission showed elevated serum creatinine (the baseline creatinine was unknown), hypoalbuminemia, and a urinalysis indicating proteinuria and hyaline casts in urine sediment. He also had a 24-hour urine test showing proteinuria in the nephrotic range (22,400 mg/24 hours) and an abnormal lipid profile with hypercholesterolemia and hypertriglyceridemia (Table 1).

A renal and urinary tract ultrasound showed normal-sized kidneys with no evidence of hydronephrosis. His signs and symptoms led to a diagnostic suspicion of rapidly progressive glomerulonephritis (RPGN), and methylprednisolone (1 g intravenously per day for three days) was started empirically while other etiological tests were performed.

His immune profile was normal, including complement C3 and C4 levels, and infectious tests were negative (Table 1). Serum protein electrophoresis revealed hypergammaglobulinemia with an elevated alpha 2 fraction and no clonal bands on serum immunofixation.

Faced with nephrotic syndrome in a young adult with significant unexplained kidney function deterioration, a kidney biopsy was performed. Twelve glomeruli were evaluated, two of which had global sclerosis. The remaining glomeruli had mild to moderate mesangial and endocapillary hypercellularity, capillary loop thickening with double contours of the basement membrane, and fibrocellular crescents (Figure 1: A, B), findings compatible with membranoproliferative glomerulonephritis with an extracapillary component.

The renal interstitium showed 50% fibrosis and tubular

Table 1. *Laboratory tests*

Laboratory tests	Values	Reference values
Proteinuria	22,400 mg	0-150 mg/dL
Serum albumin	1.70 gr/dL	3.5-5.5 gr/dL
Total cholesterol	400 mg/dL	120-200 mg/dL
Serum triglycerides	444 mg/dL	<150 mg/dL
Creatinine	3.20mg/dL	0.6-1.2 mg/dL
RPR	Non-reactive	-
Immunochromatography for HIV 1 and 2 antibodies	Negative	-
Hepatitis B (HBsAg)	0.05	<0.9
Hepatitis C antibodies	0.01	<0.9
ENAs	0.3 index	Negative
Anti-DNA	< 1/10 dils	< 1/10 dils
ANAs	Negative	< 1 index
C3	115 mg/dL	88-165 mg/dL
C4	31.70 mg/dL	14-44 mg/dL

RPR: rapid plasma reagin. HBsAg: hepatitis B surface antigen, ENAs: extractable nuclear antibodies, Dils: dilutions.

atrophy, indicating chronicity, which predicted an unfavorable response in terms of kidney function recovery. Direct immunofluorescence showed dominant C3 deposits, and electron microscopy detected electrodense intramembranous and mesangial deposits (Figure 1: B, C), confirming the diagnosis of C3GN.

The patient was subsequently treated with prednisone 30 mg by mouth per day, and mycophenolate mofetil 1 g by mouth every 12 hours, with mild improvement in serum albumin levels and 24-hour proteinuria but no significant kidney function recovery, and he was therefore discharged from the hospital (Figure 2: A, B, C, D). A new kidney biopsy was not justified, given his clinical stability.

Discussion

Complement 3 glomerulopathies are a group of rare forms of glomerulonephritis in which complement alternative pathway dysregulation results in dominant C3 deposition in the glomeruli (1, 2). They can be morphologically classified according to their ultrastructural characteristics on electron microscopy as dense deposit disease (DDD) and C3 glomerulonephritis (C3GN, first described in 2007) (3). The incidence of C3GN is estimated to be 1 to 2 cases per million inhabitants per year (1, 3).

The pathogenesis of these conditions is based on overactivation of the complement alternative pathway. Under normal conditions, low C3b levels trigger self-activation of this pathway through spontaneous C3 cleavage. Factor B then binds to properdin, forming C3 convertase (C3bBb), which amplifies the cascade through greater C3 cleavage. Well-established regulatory mechanisms exist to prevent hyperactivation of this pathway (4). These include factor H, which is responsible for fluid-phase C3 and C5 convertase decay. Factor H acts with factor I to bind to and inactivate the C3b free fraction or binds to complement receptor 1 (CR1) to inactivate cell surface-bound C3b. The alternative pathway is also regulated by other cell surface proteins like membrane cofactor protein (MCP, also known as CD46) and decay-accelerating factor (DAF, also known as CD55).

Dysregulation of the complement alternative pathway in C3GN is mostly induced by autoantibodies that stabilize C3 convertase, such as C3 nephritic factor (C3NeF), or by autoantibodies against other complement-regulating proteins (factor H, factor I, CR1, MCP, and DAF), and, less frequently, by genetic deficiencies of these proteins (5, 6). Gene C3 mutations have also been described that make activated C3 resistant to factor H-mediated inhibition or reduce its binding to CR1. As far as the prognosis, the isolated presence of C3NeF does not consistently predict a worse renal outcome.

In adult patient cohorts, the complement biomarker profiles—especially decreased serum C3 and/or increased soluble terminal complex sC5b-9—have been independently related to a higher risk of progression to kidney failure, while C3NeF positivity or negativity is not, in itself, an independent prognostic marker (7). In contrast, gene mutations that cause quantitative or functional deficiencies in complement regulators have been consistently associated with lower renal survival, higher rates of progression to end-stage renal disease, and an increased risk of post-transplant recurrence in affected patients (8).

Based on the above, a classic characteristic of C3GN is hypocomplementemia secondary to consumption by the complement alternative pathway. However, approximately 50% of patients with C3GN have been reported to have serum C3 levels within the normal range (9). This could be explained by several mechanisms: 1) complement activation occurring primarily in the glomerular microenvironment, not systemically reflected in serum levels; 2) variable presence of convertase-stabilizing autoantibodies (C3NeF is present in 80–90% of DDD cases and approximately 50% of C3GN cases) (5); and 3) mutations or variants of complement regulator proteins that create a phenotype with normal C3 serum levels. In the case we presented, given the normal serum C3 level, the most plausible hypothesis would be complement activation restricted to the kidney or the presence of alternative regulatory dysfunction mechanisms.

The diagnosis requires a kidney biopsy for histopathological studies. In most cases, light microscopy shows membranoproliferative glomerulonephritis (MPGN), although there may also be endocapillary and mesangial proliferative glomerulonephritis (10). Direct immunofluorescence (DIF) is needed to diagnose C3GN and DDD and reveal "bright" C3 deposits throughout Bowman's capsule, the glomerular basement membranes, tubules, and mesangium, with absent

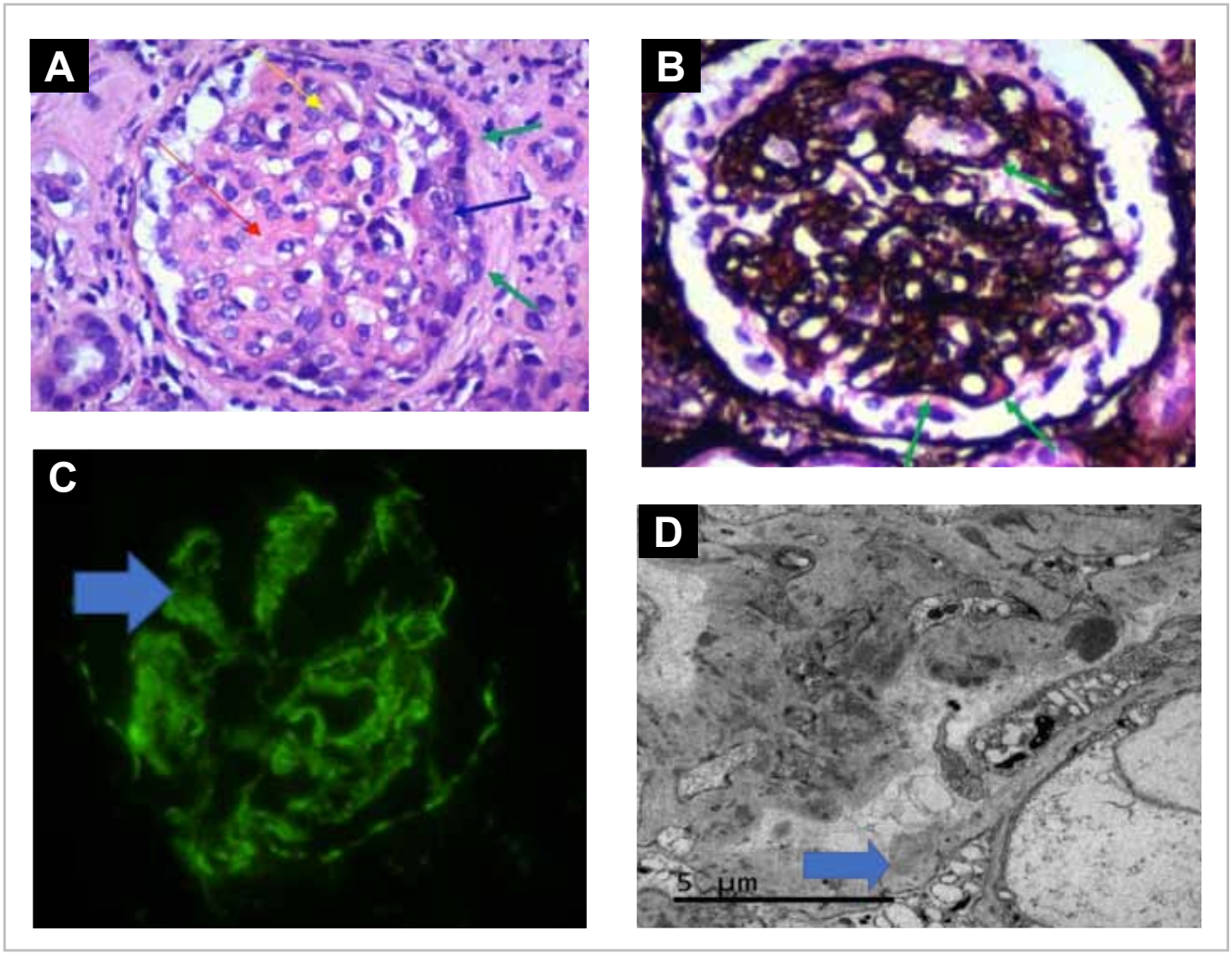


Figure 1. Histopathological findings on the kidney biopsy. A and B*: light microscopy (LM): (hematoxylin and eosin and silver methenamine stain, respectively) (original magnification x 400): A: shows marked expansion of the mesangial matrix (red arrow) along with mesangial cellular proliferation, with mesangial interposition (yellow arrow). Endocapillary proliferation can also be seen (blue arrow), as well as a partial fibrocellular crescent (green arrows),* **C***: shows a "railroad track" double contour of the GBM (green arrows),* **C***: direct immunoflourescence (DIF): conjugated anti-C3 with FITC (original magnification x 400): thick deposits are seen, predominantly mesangial, involving the capillary loop (blue arrow),* **D:** *electron microscopy (EM) (scale: 5 thousandths of a millimeter) discrete and disorganized mesangial deposits of electron-dense material (blue arrow).*

or minimal immunoglobulin deposits, suggesting that immune complexes are not involved. Electron microscopy is necessary to differentiate between the two conditions: abnormal electrodense material is found within the glomerular basement membrane, replacing and extending the lamina densa in DDD. This is not found in C3GN, where intramembranous deposits of electrodense materials may be lacking and, when present, are not limited to this location. In our case, the electrodense deposits were intramembranous and mesangial, constituting a diagnosis of C3GN because they were not limited to the glomerular basement membrane. El diagnóstico requiere la realización de una biopsia renal para estudios histopatológicos.

The treatment described in the current literature is mainly based on observational studies in America and Europe and essentially consists of the use of steroids and mycophenolate mofetil (MMF). A case series in the United States and Turkey that included 73 patients treated with different immunosuppression regimens for at least three months found that, after one year of follow-up, those treated with prednisolone and MMF had better response rates in terms of complete and partial remission compared to those treated with steroids alone or combined with calcineurin inhibitors, rituximab, or alkylating agents (11). Similarly, a retrospective, multicenter, observational study conducted in Spain by the GLOSEN group included 97 patients (DDD = 16; C3GN = 84) and demonstrated that those treated with steroids and MMF (n = 42) had higher rates of complete and partial remission, as well as less progression to advanced kidney failure, compared to other immunosuppression regimens (n = 38) or no immunosuppression (n = 17). Furthermore, the benefit of complete remission was more evident in patients

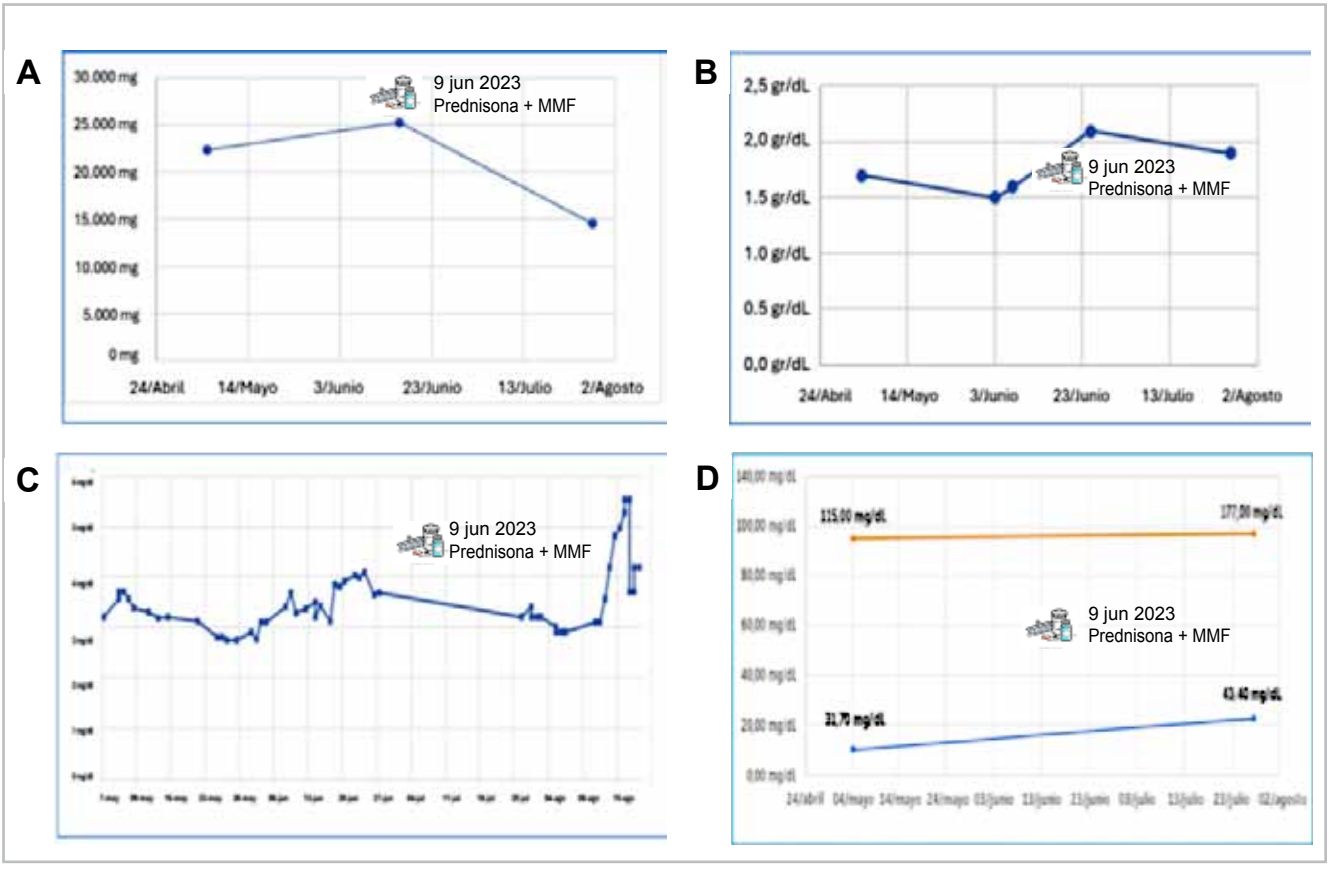


Figure 2. *Evolution of laboratory parameters before and after beginning immunosuppressant treatment (prednisone + mycophenolate mofetil) on June 9, 2023. A: 24-hour proteinuria; B: serum albumin; C: serum creatinine, D: serum complement C3 (orange) and C4 (blue) levels.*

with autoantibody-mediated pathogenic mechanisms (44 vs. 11%, p=0.03) (12).

In many C3GN cases, C3 deposits in the glomeruli lead to subsequent C5 activation, and this has allowed the use of ant-C5 antibodies, like eculizumab and ravulizumab. Nevertheless, various reviews and case series have reported variable responses to eculizumab, and therefore its use must be individualized and reserved for refractory cases or those with persistent activity despite conventional immunosuppression (13). In the patient we presented, treatment with anti-C5 antibodies was not begun due to his clinical stability, lack of progressive renal function deterioration, and partial improvement with the instated immunosuppression regimen.

However, there are limited studies available at the national and Latin American levels. In Colombia, C3GN has been documented in various clinical and pathological settings. Taborda et al. published a series of 22 cases aged 3 to 65 years, with a variety of clinical descriptions; 13.6% had rapidly progressive glomerulonephritis, and all biopsies showed proliferative glomerulonephritis. All patients had hematuria: microscopic in 86.4% and macroscopic in 13.6%. Moreover, all had proteinuria, which was sub-nephrotic in 72.7% and in the nephrotic range in 27.3%. Eight patients achieved complete remission, and six developed chronic kidney disease, five in the terminal phase (14). Nine patients had serum C3 follow-up levels, which normalized one to three months after biopsy, highlighting the importance of long-term follow-up (14).

Camacho et al. identified 27 patients with dominant C3 deposits among a group of 58 membranoproliferative glomerulonephritis cases and described their clinical-pathological findings, although they did not evaluate the therapeutic response (15). More recently, Rosselli et al. reported cases of C3GN in two pregnant women and proposed a diagnostic algorithm for C3 glomerulopathy in this context (16). An association between C3GN and Alport's syndrome has also been described (17), as well as a pediatric case successfully treated with eculizumab in the context of thrombotic microangiopathy (18).

The literature is also scarce in Latin America. In Brazil, Beirão et al. described a case of C3GN associated with monoclonal gammopathy that was treated with clone-targeting therapy, with a favorable renal response (19). In Mexico, a pediatric case of C3 membranoproliferative glomerulonephritis was reported as a "therapeutic challenge" in an oral presentation (20).

The main strength of this report lies in its detailed description of the clinical evolution and instated treatment, as well as histopathological confirmation through kidney biopsy with dominant C3 deposits. Its limitations include

the absence of complementary genetic tests, the lack of a C3NeF-sensitive functional assay due to limited access to this test in our setting, and insufficient follow-up time for evaluating long-term outcomes.

Conclusion

Complement 3 glomerulonephritis is a rare condition that is difficult to treat. Our case is a national report that provides a detailed description of the clinical and biochemical evolution under this regimen, showing a partial response to treatment. Given the presence of this disease in our setting, there is an urgent need to generate local and regional studies to systematically evaluate the effectiveness of conventional treatments.

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