

C3 Glomerulonephritis Presenting as Thrombotic Microangiopathy: A Case Report of Rare and Aggressive Phenotype

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ABSTRACT

Background: C3 glomerulonephritis (C3GN) is a rare complement-mediated glomerular disease caused by dysregulation of the alternative complement pathway. Although C3GN and thrombotic microangiopathy are distinct entities, complement overactivation may produce overlapping clinical features and create diagnostic challenges.

Case Presentation: A 37-year-old man presented with uremic symptoms, dyspnoea, altered sensorium, severe hypertension, anaemia, thrombocytopenia, and grade IV hypertensive retinopathy. Laboratory investigations revealed severe kidney dysfunction, elevated lactate dehydrogenase, markedly reduced haptoglobin, hypocomplementemia with low C3 and normal C4, proteinuria, and microscopic haematuria. However, peripheral blood smear showed no schistocytes, the reticulocyte count was 1.5%, direct Coombs testing was negative, and ADAMTS13 activity was normal. Anti-factor H antibody was also negative. Kidney biopsy demonstrated a membranoproliferative pattern with prominent lobular accentuation, diffuse endocapillary proliferation, leukocytic infiltration, and double-contour formation of the glomerular capillary walls. Approximately 50% interstitial fibrosis and tubular atrophy were present, along with tubular hemosiderin deposition. Immunofluorescence showed granular C3 deposition along the glomerular capillary loops, with negative staining for immunoglobulins, C1q, and light chains. These findings established the diagnosis of C3GN with a membranoproliferative pattern and secondary hemosiderosis. Haemodialysis was initiated because of uremic symptoms and volume overload.

Conclusion: This case highlights an aggressive C3GN presentation with a clinical phenotype suggestive of TMA, despite the absence of schistocytes and normal ADAMTS13 activity. The combination of severe hypertension, thrombocytopenia, biochemical evidence of haemolysis, hypocomplementemia, and C3-dominant renal deposits underscores the importance of integrating clinical, haematological, complement, and histopathological findings. Early recognition of this atypical presentation may help distinguish C3GN from primary TMA and guide appropriate management.

Introduction

C3 glomerulonephritis (C3GN) is a rare glomerular disease caused by dysregulated activation of the alternative complement pathway, with an estimated incidence of 1–2 cases per million population [1]. Thrombotic microangiopathy is a distinct clinicopathological syndrome characterized by endothelial injury, microvascular thrombosis, thrombocytopenia, microangiopathic haemolytic anaemia, and ischemic organ damage; its complement-mediated form, commonly classified as atypical haemolytic uremic syndrome, has an estimated annual incidence of 0.23–1.9 cases per million population [2]. Although

C3GN and TMA are separate entities, persistent alternative-pathway activation may produce a hybrid phenotype with concurrent glomerular C3 deposition and renal TMA lesions. This overlap appears to be exceptionally uncommon, having been identified in only 1 of 73 patients with TMA in one biopsy-based case series, corresponding to approximately 1% [3]. While these conditions represent distinct clinical entities, their overlapping pathophysiology driven by uncontrolled complement activation can result in complex diagnostic challenges when C3 glomerulonephritis manifests with concurrent features of thrombotic microangiopathy [4,5].

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This overlap may follow a severe renal course, with some patients achieving hematologic and partial renal remission after complement-directed therapy, while others progress to advanced kidney failure despite treatment [3]. However, because the condition is rare, its long-term renal prognosis remains uncertain, and prolonged monitoring is required for recurrent complement-mediated injury and progression to end-stage kidney disease [6]. Therefore, integrating clinical, hematologic, complement, and renal biopsy findings is essential for recognizing this hybrid phenotype and guiding appropriate management [3,6].

Case History

A 37-year-old male presented with nausea and intermittent vomiting for 10 days, decreased appetite for 10 days, difficulty breathing for 2 days, altered sensorium for 1 day. There was no history of fever, oliguria, visible haematuria, diarrhoea, abdominal pain, arthralgia, oral ulcers, photosensitivity, jaundice, skin rashes, blurring of vision, weight loss, analgesic use. There was no history of any systemic illness or comorbidity. There was no family history of hypertension, diabetes mellitus, kidney disease. On examination patient was dyspnoeic and drowsy responding to deep pain and blood pressure was 160/90mm Hg with Pulse rate of 96 beats /min with respiratory rate of 22/min. There was pallor and bipedal edema. Respiratory examination revealed bilateral basal crepitations. Fundus showed Grade IV hypertensive retinopathy changes. Urine dipstick revealed 3+ proteinuria with 10-12 RBC's /HPF. Laboratory investigations demonstrated severe azotaemia, anaemia, thrombocytopenia, elevated LDH, hyperuricemia, hypocalcaemia, hyperphosphatemia and hyponatremia. Peripheral blood smear showed no schistocytes and Reticulocyte count was 1.5%. Immunological evaluation showed weakly positive ANA (1:100) with negative ANA blot, negative cANCA and pANCA. serum C3 was reduced (60mg/dl), whereas serum C4 was normal (23mg/dl). Direct Coombs test was negative. serum haptoglobin was markedly reduced at 0.1. ADAMTS13 activity was normal (0.06%). Anti Factor H Antibody was negative. 2D Echocardiography showed concentric LVH, Ejection Fraction of 60% with mild mitral and tricuspid regurgitation. Serum protein electrophoresis was negative. Thyroid profile was within normal limits. USG Abdomen and pelvis revealed normal sized kidney

with increased echogenicity and maintained corticomedullary differentiation. He underwent Haemodialysis in view of uremic symptoms and volume overload.

Native Kidney Biopsy was done. 10 glomeruli were seen. one glomerulus was globally sclerosed. The viable glomeruli demonstrated prominent lobular accentuation with diffuse endocapillary proliferation and leucocytic infiltration. Glomerular capillary lumen were diffusely obliterated and capillary walls demonstrated a double contour appearance. No crescents or fibrinoid necrosis was seen. There was moderate to severe tubular injury and tubular atrophy with approximate 50 % interstitial fibrosis and tubular atrophy. Patchy interstitial lymphocytic infiltration and coarse brown pigment within tubular epithelial cells were noted. Vascular examination showed mild hyperplasia of tunica media and intimal fibroplasia without evidence of vasculitis or luminal thrombosis.

Immunofluorescence demonstrated granular C3 deposition along the glomerular capillary loops while IgG, IgA, IgM, C1 q, kappa and lambda light chains was negative. No extra glomerular deposits were identified.

The overall finding was consistent with C3 mediated Glomerulonephritis with a Membranoproliferative Glomerulonephritis pattern with secondary hemosiderosis.

Genetic evaluation, including clinical exome sequencing and MLPA for CFH/CFHR1-5 deletion/duplication analysis, revealed no pathogenic or likely pathogenic variants associated with complement-mediated glomerulopathy.

The patients was treated with steroids and mycophenolate mofetil after which patient improved and did not require further haemodialysis. However patient was lost to follow up and stopped all medications, presented again to emergency after 6 months with uremia and pulmonary edema. Patient underwent urgent hemodialysis and was evaluated further for acute causes of renal dysfunction which were found to be negative. He was continued on supportive management for chronic kidney disease and now on regular haemodialysis of twice weekly sessions. The patient was registered on the transplant list and work up is being done.

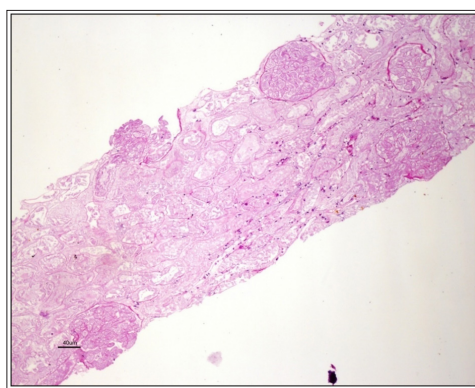
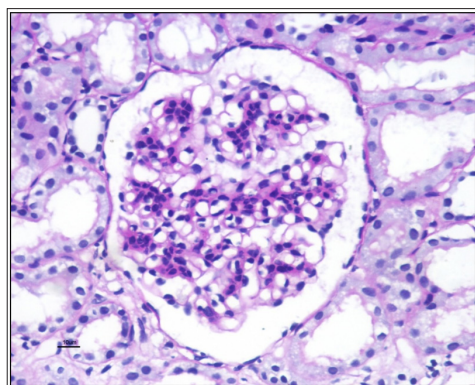
Table 1: laboratory Investigations

Haemoglobin (g/dl)	8.6
Total leucocyte count (/μL)	6570
Total platelet count(/μL)	57000
Peripheral blood smear	Anisocytosis, target cells seen, Schistocytes absent
Reticulocyte count	1.5%
Serum LDH(U/L)	1333
ESR (mm)	91
Serum urea (mg/dL)	290
Serum Creatinine(mg/dL)	10.97
Proteinuria (gm/24hours)	2.9
Urine analysis	Protein – 3+, RBC- numerous/HPF
Serum C3(mg/dL)	60
Serum C4(mg/dL)	23
Direct Coombs test	Negative

Indirect coombs test	Negative
Serum haptoglobin(mg/dL)	0.1
ADAMTS-13 Activity (IU/mL)	0.6
Anti Factor H antibody (AU/mL)	24

Table 2: Summary of Molecular Genetic Analysis

Parameter	Finding
Specimen	Peripheral blood
Genetic test	Clinical-exome sequencing, MLPA for detection of CNV
Variants assessed	Single-nucleotide variants, small insertions/deletions, and copy-number variants
Clinical-exome result	No pathogenic or likely pathogenic variants relevant to the renal phenotype were identified; no reportable copy-number variants were detected.
Complement-gene deletion/duplication analysis	No deletions or duplications detected in CFH or CFHR1–CFHR5.
Overall interpretation	No definitive molecular diagnosis was established.

**Figure 1:** Light microscopy showing acute tubular necrosis (low power)**Figure 2:** Glomerular changes in membranoproliferative glomerulonephritis. H&E staining demonstrates a hypercellular, lobulated glomerular tuft with prominent mesangial and endocapillary cellularity and narrowing of the glomerular capillary lumina, consistent with a membranoproliferative pattern of glomerular injury. (high power)

Discussion

C3 glomerulopathy (C3G) is a complement-mediated renal disease characterized by predominant glomerular deposition of C3 in the absence of significant immunoglobulin deposition. It comprises C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), which are distinguished primarily by their ultrastructural characteristics. The underlying pathophysiology is dysregulation of the alternative pathway

of complement, resulting in excessive complement activation and glomerular injury [7,8]. In the present case, the renal biopsy demonstrated C3-mediated glomerulonephritis with an MPGN pattern, characterized by prominent endocapillary proliferation, leukocytic infiltration, capillary wall double contours, and dominant granular C3 deposition with negative immunoglobulins and C1q. These findings fulfil the pathological criteria for C3G and illustrate that C3G may present with a variety of light microscopic patterns, including an MPGN pattern [7,8]. Importantly, the diagnosis of C3G is primarily based on the immunofluorescence pattern, while the light microscopic appearance may be variable [8].

The patient had reduced serum C3 with preserved C4, supporting activation of the alternative complement pathway. Complement dysregulation in C3G may result from acquired autoantibodies, particularly C3 nephritic factors and antibodies directed against complement regulatory proteins, or from genetic abnormalities involving components and regulators of the alternative pathway, including C3, CFB, CFH, CFI, and CFHR genes [7,9]. In the present patient, anti-factor H antibody was negative, while genetic evaluation, including clinical exome sequencing and CFH/CFHR1–5 deletion/duplication analysis, failed to identify a pathogenic or likely pathogenic variant.

A negative genetic evaluation, however, does not exclude C3G. In a cohort of 134 patients with C3G and related MPGN phenotypes, both acquired and genetic abnormalities of the complement pathway were identified, but no single abnormality accounted for the majority of cases [9]. Thus, the absence of an identifiable genetic defect in our patient does not negate the diagnosis established by renal biopsy and complement profile. The current understanding of C3G supports a multifactorial model in which genetic susceptibility and acquired complement abnormalities may interact to produce disease [8,9].

An important feature of this case was the presence of thrombocytopenia, markedly elevated LDH, and low haptoglobin, raising the possibility of a thrombotic microangiopathy (TMA).

However, peripheral blood smear showed no schistocytes, ADAMTS13 activity was within the reported reference range, and renal biopsy did not demonstrate luminal thrombosis or definitive vascular TMA. Therefore, the available findings are more appropriately described as a TMA-like clinical and biochemical phenotype rather than definite renal TMA.

The distinction is particularly relevant because severe hypertension itself can produce endothelial injury and a secondary TMA phenotype, characterized by thrombocytopenia and microangiopathic haemolysis. Conversely, complement-mediated TMA, including atypical haemolytic uremic syndrome, can present with severe hypertension and predominant renal involvement [10]. In our patient, the presence of grade IV hypertensive retinopathy and marked concentric left ventricular hypertrophy provides evidence of significant hypertensive target-organ injury. Thus, severe hypertension may have contributed to the haematological abnormalities and renal endothelial injury. Nevertheless, the dominant biopsy lesion was glomerular C3-mediated disease rather than TMA.

The coexistence of C3GN and TMA-like features is biologically plausible because complement dysregulation is implicated in both disorders. However, the renal pathological manifestations differ: C3GN is characterized predominantly by complement deposition within glomeruli, whereas TMA is characterized by endothelial injury involving the renal microvasculature [8–10]. In this case, the absence of definitive vascular TMA on biopsy, together with the absence of schistocytes and normal ADAMTS13 activity, favours C3GN as the primary renal disease, with severe hypertension and/or complement-mediated endothelial injury potentially accounting for the TMA-like phenotype.

The biopsy also demonstrated approximately 50% interstitial fibrosis and tubular atrophy, moderate-to-severe tubular injury, and vascular changes including arteriosclerosis and hyaline arteriolosclerosis. Repeat Ultrasonography showed relatively small, echogenic kidneys, further suggesting significant chronicity. These findings are clinically important because established tubulointerstitial and vascular injury may limit the potential for renal recovery despite control of the underlying complement-mediated process. In a cohort of 80 patients with C3G, 29% progressed to end-stage kidney disease during a median follow-up of 28 months, with histological and clinical characteristics helping to identify patients at increased risk of poor renal outcome [11].

The management of C3GN remains challenging because of its heterogeneous pathogenesis and the limited evidence base for treatment. Supportive therapy, including optimal blood pressure and proteinuria control, remains fundamental. KDIGO guidelines recommends consideration of mycophenolate mofetil with glucocorticoids for patients with moderate-to-severe C3GN in the absence of monoclonal gammopathy, with consideration of complement inhibition in treatment-resistant disease [12]. The optimal treatment should, however, be individualized according to the severity of active disease, degree of chronicity, complement abnormalities, and renal function.

The present case is particularly noteworthy because the patient initially required dialysis, subsequently had dialysis withheld after treatment, but later discontinued medications and was lost to follow-up before returning with worsening renal dysfunction. This clinical course emphasizes the progressive nature of C3GN and the importance of long-term nephrology follow-up.

Conclusion

This case highlights an unusual presentation of biopsy-proven C3 glomerulonephritis with a MPGN pattern associated with severe hypertension and a TMA-like hematological phenotype. The combination of dominant C3 deposition, reduced C3, negative immunoglobulin staining favours the diagnosis of C3GN. The concurrent thrombocytopenia, elevated LDH, and low haptoglobin warranted evaluation for TMA; however, the absence of schistocytes, normal ADAMTS13 activity, and lack of definitive renal TMA favored C3GN with a TMA-like phenotype rather than established TMA. The case underscores the importance of integrating clinical, hematological, complement, and renal histopathological findings when evaluating patients with severe kidney dysfunction and suspected complement-mediated disease.

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