Case Report

C3 Glomerulonephritis at the crossroads of Diabetes and Renal Failure: A Case Report

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ABSTRACT

C3 glomerulopathy (C3G) is a rare complement-mediated kidney disease characterized by dominant C3 deposition in the glomeruli, with C3 glomerulonephritis (C3G) and dense deposit disease (DDD) as its two main subtypes. We present the case of a 66-year-old female with known C3G on maintenance hemodialysis, complicated by diabetes, hypertension, and diabetic foot ulcer. She had large hematuria, significant proteinuria, severe renal failure, and a noticeably increased serum creatinine level. In addition to early diabetic nephropathy and chronic renal alterations, kidney biopsy confirmed C3GN with a diffuse endocapillary proliferative pattern, crescent development, significant C3 deposition, and lack of immunoglobulins. Hemodialysis, antihypertensives, steroids, renal-supportive drugs, and insulin treatment were used to treat her. In addition to highlighting the difficulties in treating advanced C3G, this case adds to the limited information on this rare illness and underscores the diagnostic value of kidney biopsies.

Key words: C3 glomerulopathy, C3 glomerulonephritis, Complement pathway, Chronic kidney disease, Kidney biopsy.

The term "C3 glomerulopathy" (C3G) denotes a glomerulonephritis with isolated or dominant C3 staining that implies an etiology rooted in dysregulation of the alternative complement pathway [1-4]. However, this criterion was over-stringent and recently it has been suggested that C3G is more appropriately identified by selecting glomerular changes in which there is "C3 dominant" staining. C3 dominant is defined as C3 intensity at least two orders of magnitude greater than any other immune reactant. The 2 patterns of C3G are C3 glomerulonephritis (C3G) and dense deposit disease (DDD). DDD is defined by the EM findings of intramembranous glomerular basement membrane dense deposits, and C3GN encompasses the remainder of the C3G lesions and is defined by some combination of mesangial, subepithelial, subendothelial, and/or less dense, discontinuous intramembranous deposits [5-8].

On histopathology, C3G was originally described as a disease characterized by C3 staining in absence of C1q, C4, and immunoglobulins on immunofluorescence (IF) microscopy; newer definitions allow for the presence of some immunoglobulin if C3 staining is dominant and at least 2 orders of magnitude greater than any other immunoreactant [9-12]. Registry data on C3G suggest a prevalence in the United States of about 2-3 cases per 1,000,000. In Europe, the incidence is thought to be lower with approximately 0.2- 1.0 cases per 1,000,000 [5]. Clinically, C3G presents with proteinuria, haematuria, and often some degree of renal failure [9]. The most common histologic finding on light microscopy is membranoproliferative glomerulonephritis, although similar C3-dominant staining and deposits (presumably of complement components) in the mesangial, subepithelial, subendothelial, and intramembranous regions of the glomerulus have also been demonstrated in patients with mesangial proliferative or diffuse endocapillary proliferative patterns [1]. This case report intends to provide a comprehensive clinical and pathological description of a 66-year-old woman with advanced C3 glomerulonephritis (C3GN) undergoing haemodialysis, complicated by diabetes, hypertension, and a diabetic foot ulcer. The report emphasizes the diagnostic importance of kidney biopsy exhibiting predominant C3 deposition and crescentic glomerulonephritis, addresses the difficulties in management, and adds to the scarce understanding of this uncommon, advancing complement-mediated renal condition.

CASE PRESENTATION

A 66-year-old female was admitted with complaints of progressive breathlessness and generalized weakness for three days. She has a documented history of C3 glomerulonephritis

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(C3GN) on maintenance haemodialysis. She is also a known case of type 2 diabetes mellitus and hypertension, and presented concurrently with a left diabetic foot ulcer. Notably, there was no history of fever, chest pain, or burning micturition, but she did present with significant pedal edema. Laboratory investigations highlighted significant renal impairment, her serum urea was 170.6mg/dL and creatinine were 10.62mg/dL, confirming her advanced renal failure. She had persistent hyperuremia evidenced by urea 190.8mg/dL and creatinine 10.78mg/dL during her hospitalization. Electrolyte disturbances included hyponatremia (sodium 124.7mmol/L) and episodes of variable potassium levels (3.33-4.29mmol/L). Her hemogram was also abnormal, with haemoglobin of 8.1g/dL, haematocrit 24.3%, and a marked thrombocytopenia (platelets = 0.77 lakh/mm^3), the peripheral smear revealing normocytic normochromic anaemia with thrombocytopenia.

Kidney biopsy revealed ten glomeruli, of which four were obsolete. The viable glomeruli exhibited a diffuse endocapillary proliferative pattern with crescent formation observed in up to five glomeruli, without evidence of necrosis or vasculitis. The tubulointerstitial compartment showed patchy edema, mild tubular atrophy, and approximately 25% interstitial fibrosis with lymphocytic infiltration, indicating chronic damage. Immunofluorescence demonstrated strong, diffuse, coarse granular C3 (3+) deposition along the glomerular capillary walls and mesangium, with negative staining for immunoglobulins and light chains. These findings are consistent with complement C3-mediated glomerulonephritis (C3GN) exhibiting a diffuse endocapillary crescentic pattern, alongside early diabetic nephropathy (Class IIb) and moderate chronic renal injury, contributing to the patient's progression to end-stage renal disease. She received hemodialysis as required and was managed medically for her comorbidities and complications. Her treatment regimen included:

Antihypertensives	Tab. Amlong BD
	Tab. Dytor 20 mg BD
Renal Supportive therapy	Tab. Renolife OD
	Tab. Sobosis EC 500 mg BD
Steroids	Tab. Wysolone 50 mg OD
Insulin	H. Mixtard
	Insugen

DISCUSSION

C3 glomerulopathy(C3G) refers to a group of rare order conditions associated with dysregulation of the indispensable complement pathway. The 2 patterns of C3G are C3 Glomerulonephritis (C3G) and thick deposit complaint (DDD) [5]. The annual incidence of biopsy-proven disease is 1 to 2 per million [9]. Dysregulation of any component of this pathway can result in the development of disease, including atypical haemolytic uremic syndrome and age-related macular degeneration [13]. The kidney is especially susceptible to complement-mediated injury, most commonly triggered by immune complex deposition and activation of the complement classic pathway Traditionally, this was in the setting of the absence or near absence of immunoglobulins.

However, this criterion was over-stringent and recently it has been suggested that C3G is more appropriately identified by selecting glomerular changes in which there is “C3 dominant” staining. C3 dominant is defined as C3 intensity at least two orders of magnitude greater than any other immune reactant. Clinically, C3G manifests as haematuria, proteinuria, and frequently some level of renal failure. Our patient, presented with severe renal dysfunction, heavy proteinuria (3+), gross haematuria (3+), RBC casts, and markedly elevated serum creatinine (15.53 mg/dL) which aligns with the clinical presentation of C3 glomerulopathy (C3G), which is typically characterized by proteinuria, haematuria, and varying degrees of renal dysfunction. This presentation is consistent with the findings reported by *Xue Xiao et al.* [9]. Given the vagueness of the donation and oddity of complaint, it can be challenging for the clinician to consider C3G in the discriminational opinion prebiopsy.

Although the first step in the diagnostic workup is usually serological testing, which will result in low C3 levels in approximately two-thirds of C3G cases, definitive diagnosis requires kidney biopsy [5]. Our patient underwent a kidney biopsy, which provided definitive diagnostic confirmation of C3 glomerulonephritis (C3GN). Histopathological examination revealed ten glomeruli, of which four were globally sclerosed, while the remaining glomeruli showed a diffuse endocapillary proliferative pattern with crescent formation in up to five glomeruli. The tubulointerstitial compartment demonstrated patchy edema, mild tubular atrophy, and approximately 25% interstitial fibrosis with lymphocytic infiltration, consistent with chronic damage. Immunofluorescence revealed strong, diffuse, coarse granular C3 (3+) deposition along the glomerular capillary walls and mesangium, with negative staining for immunoglobulins and light chains, confirming complement-mediated injury.

These findings are characteristic of C3GN with a diffuse endocapillary crescentic pattern, accompanied by early diabetic nephropathy (Class IIb) and moderate chronic renal injury which aligns with the findings of *Sanjeev Sethi et al.* [14,15]. There is currently no broadly effective targeted treatment option for C3G and, as a consequence, a variety of supportive measures have been used. In a French cohort, treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has shown to improve renal survival [5]. In this case she received haemodialysis as required and was managed medically for her comorbidities and complications. Her treatment regimen included antihypertensives (Tab. Amlong BD, Tab. Dytor 20 mg BD), Renal-supportive therapy (Tab. Renolife OD, Tab.

Sobosis EC 500 mg BD), and steroids (Tab. Wysolone 50 mg OD), and regular insulin (H. Mixtard and Insugen). If diagnosed later in the disease course, patients can present with episodes of acute kidney injury and chronic kidney disease [5]. Early recognition and supportive management remain essential to slow disease progression and improve outcomes.

CONCLUSION

This case highlights the diagnostic and therapeutic challenges of C3 glomerulonephritis (C3G), a rare complement-mediated kidney disease that often presents with nonspecific symptoms but carries a high risk of progression to end-stage renal disease. The definitive diagnosis was established through kidney biopsy, which demonstrated dominant C3 deposition with a diffuse endocapillary crescentic pattern, chronic renal injury, and coexisting early diabetic nephropathy. Despite the absence of effective targeted therapies, timely recognition, supportive care, and haemodialysis were crucial in managing complications and stabilizing the patient's condition. This report emphasizes the importance of early biopsy, multidisciplinary care, and further research to improve diagnostic precision and therapeutic strategies in C3GN.

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