

Single Case

# Complete Renal Recovery in Pediatric Patient with C3 Glomerulonephritis: A Case Report

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## Keywords

C3 glomerulonephritis · Complement system · C3 nephritic factor · Proteinuria · Mycophenolate mofetil

## Abstract

C3 glomerulonephritis (C3GN) is a rare kidney disease resulting from dysregulation of the alternative complement cascade. Without treatment, approximately 70% of affected children and 30–50% of affected adults will develop worsening of proteinuria and progress to end-stage renal disease within 10 years of diagnosis. Here, we describe a 9-year-old Sudanese girl with no significant past medical history who presented to the Emergency Department with a 2-month history of fatigue, poor oral intake, and worsening facial and lower extremity edema, and subsequently found to have anemia, hypoalbuminemia, microscopic hematuria, and proteinuria. Additional laboratory testing revealed that the patient had low C3, high C3 nephritic factor (C3NeF), and high factor H. Renal function was normal. The diagnosis of C3GN was confirmed by renal biopsy. The patient was treated with ACE inhibitor, mycophenolate mofetil (600 mg per m<sup>2</sup> per dose, every 12 h), in combination with “pulse” methylprednisolone at 30 mg/kg/day IV bolus (maximum 1 g) for 3 consecutive days, followed by 2 months of daily oral prednisolone (2 mg/kg/day) and alternate-day prednisolone weaning from 1 mg/kg to 0.1 mg/kg for additional 12 months. Mycophenolate was continued throughout her treatment course and for maintenance therapy. In response to treatment, anemia, microscopic hematuria, hypoalbuminemia, and proteinuria resolved. Complete complement profile before and at 6 months therapy showed normalization of C3NeF, complement regulatory factor H and C3. This present case provides evidence of the full responsiveness of a rare form of complement dysregulation C3GN to a combination of mycophenolate and corticosteroids. The disease has NOT recurred in >2 years after initial presentation.

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## Introduction

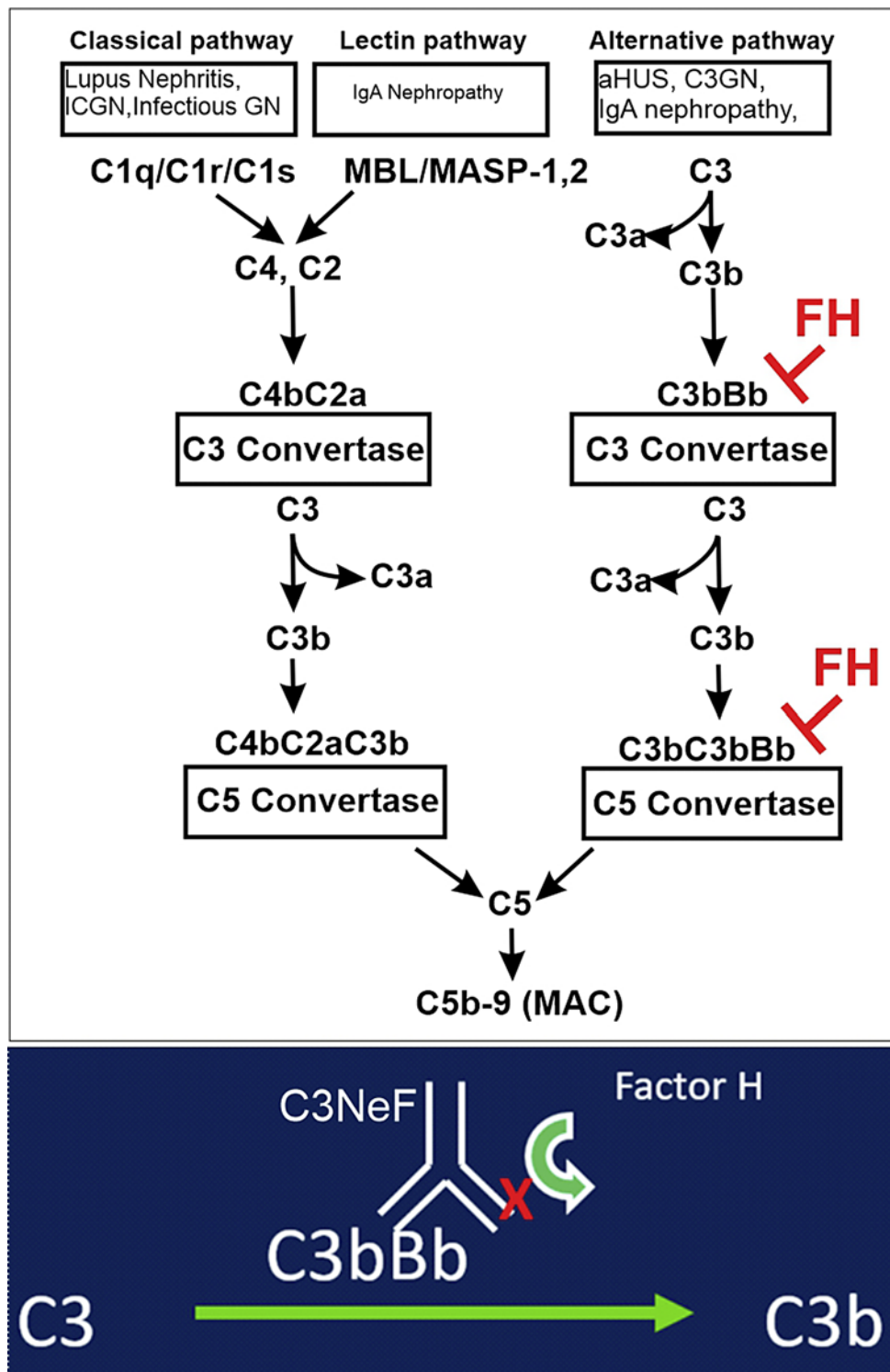
C3 glomerulopathy describes a group of rare kidney diseases caused by abnormal regulation of the complement cascade and is characterized by predominant glomerular C3 fragment deposition with electron-dense deposits on electron microscopy. The current definition of C3 glomerulopathy is based on the underlying pathogenesis of alternative complement pathway (AP) dysregulation and is further subdivided into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) based on EM findings. The AP is normally tightly regulated and activation results in the formation of C3 convertases (C3bBb), which amplifies the complement cascade. Dysregulation of the AP cascade can be caused by either mutations or autoantibodies directed at C3bBb and other AP components, leading to subsequent glomerular injury [1]. Acquired causes of C3 glomerulopathy include the formation of autoantibodies such as C3 nephritic factors (C3NeF), anti-factor B autoantibodies, and anti-factor H autoantibodies. Factor H normally inhibits C3bBb, and antibodies generated against factor H may block its inhibitory action. C3NeF are autoantibodies generated to C3bBb that also block the inhibitory actions of factor H, thereby preventing normal breakdown of C3bBb, resulting in C3 consumption and deposition. Genetic causes of C3 glomerulopathy are most commonly related to the loss of functional factor H or other complement components such as factor I and membrane cofactor protein. In the presence of autoantibodies and/or genetic mutations in complement components, the AP is “always on” (shown in Fig. 1) [2].

Clinical evaluation typically shows classic signs and symptoms of glomerulonephritis including proteinuria, hematuria, and hypertension. Measurement of complement C3 and C4, and screening for autoantibodies can identify complement dysregulation in most patients. Subsequent renal biopsy and IF may distinguish C3 glomerulopathy from immune-complex glomerulonephritis by the absence of significant immunoglobulin deposits. There are 2 major subgroups of C3 glomerulopathy-DDD and C3GN. Although it is difficult to distinguish these 2 subgroups based on light microscopy and immunofluorescence, on EM, C3GN is characterized by mesangial and subendothelial electron-dense deposits, whereas DDD is characterized by an unusual electron-dense appearance transforming the lamina densa of the glomerular basement membranes (GBMs). Thus, EM findings are required to confirm the diagnosis of C3GN [3].

C3GN affects both children and adults, with an incidence estimated to be between 1 and 3 cases per 1,000,000 in the United States. Without treatment, approximately 70% of affected children and 30–50% of affected adults will progress to end-stage renal disease within 10 years of diagnosis [4]. Due to the rarity of the disease, optimal treatment has not yet been established, with no randomized trials to inform therapeutic decisions [3]. Here, we describe a case of pediatric C3GN who had high level of C3NeF, and proteinuria. Treatment with Angiotensin-converting-enzyme inhibitor (ACEi), mycophenolate mofetil (MMF), and steroids resulted in complete renal recovery.

## Case Report

A 9-year-old girl originally from Sudan presented to the Emergency Department at Oishei Children’s Hospital in April 2018 with a 2-month history of fatigue, poor oral intake, and swelling of the face, hands, and feet. She was previously in good health with no recent illnesses or significant past medical history. Review of systems was positive for mild SOB, dry mouth, and multiple teeth caries, but revealed no chest pain, cough, myalgias, bleeding, or spontaneous bruising. She denied any recent cough, congestion, sore throat, or rhinorrhea. Family history was negative for bleeding disorders, rheumatologic disorders, autoimmune disorders,



**Fig. 1.** Complement pathways in the kidneys. Upper: common complement cascades. Lower: C3NeF, which is an antibody that combines with the C3bBb and prevents its catabolism, leading to AP dysregulation. This allows AP to be “always on.” ICGN, immune complex glomerulonephritis; aHUS, atypical hemolytic uremic syndrome; AP, alternative complement pathway; C3NeF, C3 nephritic factor; C3bBb, C3 convertase.

**Table 1.** Biochemistry profile at the time of diagnosis

Blood tests	At the time of diagnosis	Reference ranges
Serum creatinine, mg/dL	0.68	0.4–1.0
Albumin, g/dL	2.5	3.5–5
ESR, mm/h	122	0–12
CRP, mg/L	30	0.2–10
C3, mg/dL	37	80–175
C4, mg/dL	19.5	14–40
Iron panel, mcg/dL (%)	Iron 38 (Tsat 12)	Iron 30–185 (Tsat 20–55)
Coagulation panel, s (%)	PTT 41.5 (XII activity 37)	PTT 25–34 (XII activity 55–135)
RNP	Positive	Negative
SSA, SSB	Positive	Negative
Histone	Positive	Negative
Urine test		
Proteinuria, mg/h	1,120/24	0–150/24
Hematuria	RBC 6–25/hpf	RBC 0–2/hpf

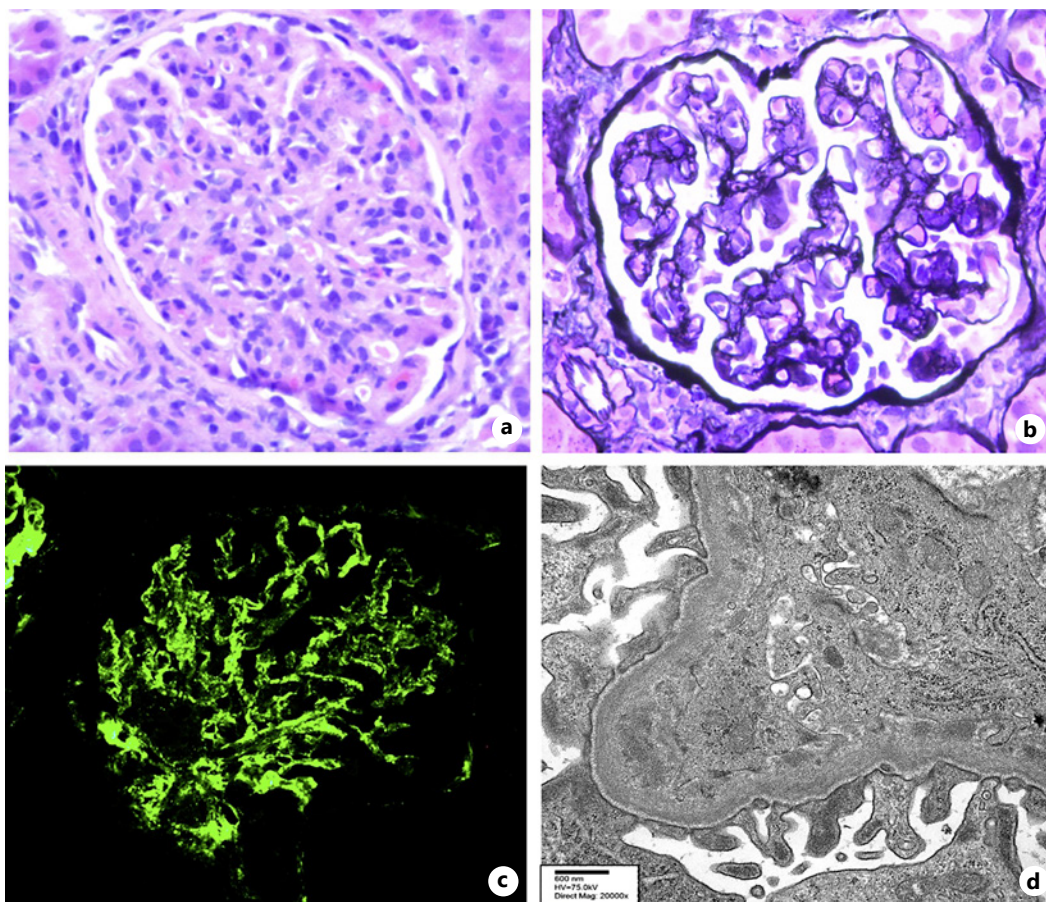
Patient had normal serum creatinine. She had hypocomplementemia (C3), proteinuria, hematuria, anemia with iron deficiency, and factor XII deficiency. She had positive autoantibodies to SSA, SSB, and RNP. Serum creatinine was normal. ANA, rheumatoid factor; anti-GBM antibody, Lupus panel (anti-SM, an-dsDNA), vasculitis panel (C-ANCA, P-ANCA, and MPO), viral panel (HIV, Hepatitis B&C, and EBV) were negative. SSA, Sjögren's-syndrome-related antigen A; SSB, Sjögren's-syndrome-related antigen B; RNP, ribonucleoprotein; anti-GBM, anti-glomerular basement membrane.

anemias, or kidney disease. On examination, she was febrile ( $T_{\max}$  38.1°C), with a blood pressure of 116/67 mm Hg. Physical exam was significant for mild periorbital edema, and swelling of the right hand and right ankle, but was otherwise unremarkable. Imaging was significant for bilateral pleural effusion on chest X-ray. Echocardiogram showed small pericardial effusion.

Blood work revealed anemia (Hgb 7.4 g/dL) with low iron and high ferritin (iron 38 mcg/dL, Tsat 12%, and ferritin 255 ng/mL), negative coombs test, hypoalbuminemia (albumin 2.5 g/dL), microscopic hematuria (RBC 6–25/hpf), and proteinuria (1,120 mg/24 h and urine p/c ratio = 1). Kidney function was normal (eGFR >100 mL/min/1.73 m<sup>2</sup>). Rapid strep test as well as blood and throat cultures were negative. Additional laboratory testing revealed elevated inflammatory markers (ESR 122, CRP 30), low CH 50 <13 unit/mL (nL 42–95 unit/mL), low complement C3 (37 mg/dL, nL 88–220 mg/dL), elevated C3NeF (131.3 unit/mL, nL ≤0 unit/mL), and normal C4. Otherwise, ANA, RF, peripheral and cytoplasmic antibodies, antibodies to GBM, and rest of Lupus panel (ENA smith, anti-dsDNA) were negative (shown in Table 1).

Patient underwent kidney biopsy which showed endocapillary proliferative glomerulonephritis (shown in Fig. 2A, B). Immunofluorescence revealed isolated, strong granular/chunky C3 staining in the mesangium and along the GBMs, with no immunoglobulin deposits (shown in Fig. 2C). Electron microscopy showed variable-sized electron-dense deposits in the mesangium and subendothelial regions (shown in Fig. 2D). There is no band-like electron-dense material along the lamina densa as commonly seen in the DDD. Systemic lupus erythematosus, Sjogren's syndrome, mixed connective tissue disease, and cryoglobulinemia were ruled out.

A diagnosis of C3GN was made in combination with the clinical and molecular test findings. The patient was treated with ACE inhibitor (enalapril maleate, 5 mg/day), MMF (600 mg per m<sup>2</sup> per dose, every 12 h), and a combination of “pulse” methylprednisolone at 30 mg/kg/day IV bolus (maximum 1 g) for 3 consecutive days, followed by 2 months of daily oral

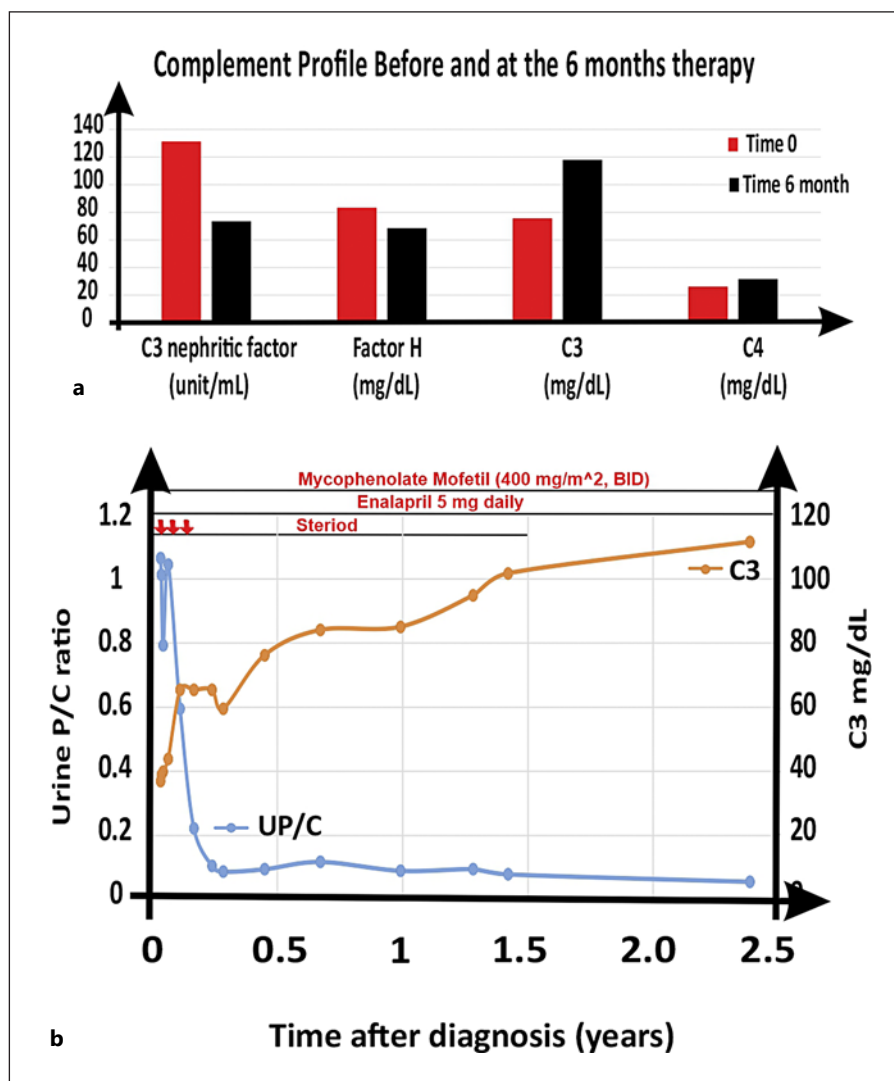


**Fig. 2.** Renal biopsy. The glomerulus shows endocapillary hypercellularity in a lobular pattern (A) with occasional GBM double contours appreciated on Jones silver stain (B). On immunofluorescence, there are diffuse, chunky C3 deposits in the mesangium and segmentally along the capillary loops (C), whereas immunoglobulin stains are all negative (not shown). On electron microscopy, variable-sized electron-dense materials are seen in the mesangium and subendothelial regions (D). GBM, glomerular basement membrane.

prednisolone (2 mg/kg/day) and alternative-day prednisolone weaning from 1 mg/kg to 0.1 mg/kg for an additional 12 months. The patient continued mycophenolate 600 mg per m<sup>2</sup> per dose, every 12 h throughout her treatment course and as maintenance therapy after the completion of steroids. One month into therapy, C3 levels remained low (66 mg/dL) with persistence of proteinuria and microscopic hematuria, despite improvement (shown in Fig. 3B). Six months into therapy, C3NeF improved to 73.5 unit/mL (44% reduction), with complete resolution of proteinuria, hypoalbuminemia, microscopic hematuria, and anemia. C3 and complement regulatory factor H returned to normal (shown in Fig. 3A, B). The disease has not recurred in >2 years after initial presentation (shown in Fig. 3B).

## Discussion

C3GN is a rare and complex renal disease due to complement dysregulation. Uncontrolled complement activation leads to progressive glomerular inflammation and scarring with eventual chronic and irreversible damage that portends end-stage renal disease. Clinical presentations typically include proteinuria and hematuria in association with low C3 level



**Fig. 3. A** Complete complement profile before and at the 6 months of therapy. Of note, C3NeF was significantly reduced. C3 and complement regulatory factor H normalized within 6 months. **B** Time course showing normalization of C3 levels and complete resolution of proteinuria in response to treatment. Of note, patient was treated with ACEi, mycophenolate, and a combination of “pulse” and oral steroid which was tapered off within 15 months. ACEi and mycophenolate are continued. The disease has NOT recurred in 2 and half years after initial presentation. The red arrows indicate steroid pulse  $\times 3$ . C3NeF, C3 nephritic factor; ACEi, angiotensin-converting-enzyme inhibitor.

and presence of autoantibodies against complement pathway molecules or regulators, suggesting a disorder of the complement cascade via the alternative pathway [2]. C3NeFs are the most common autoantibody seen in C3GN, being detected in  $\sim 50\%$  of patients [5]. Other complement regulatory proteins that may be seen in C3GN include C5 Nephritic Factor, C4 Nephritic factor, Factor H, and Factor B. Together, identification and measurement of these autoantibodies along with complement regulatory proteins may serve as a biomarker to monitor the course of the disease and potentially guide treatment decisions [3]. In the present case, C3NeF was significantly elevated on initial presentation and declined after treatment, concurrent with improvement in clinical symptoms (proteinuria) and normalization of complement C3 levels. Further studies are necessary to characterize the prognostic utility of

Nephritic Factors, as they exhibit significant interindividual variation in levels, types, and activities.

This case highlights the challenge of definitively diagnosing C3GN, as clinical and diagnostic findings may overlap with a number of rheumatologic and hematologic conditions. The diagnosis of Lupus nephritis was considered before renal biopsy, as the patient demonstrated multiple features of SLE (serositis/pleural effusions, low C3, and positive anticardiolipin antibodies). However, ANA was negative and immune complex deposition characteristic of lupus nephritis was absent, and repeated anticardiolipin antibodies were negative. Cryoglobulinemia was excluded based on negative cryoglobulin tests, a negative viral panel (hepatitis C antibody) and the absence of thrombus-like endothelial deposits on LM. Post-infectious glomerulonephritis (PIGN) and paraprotein-associated glomerulonephritis may also exhibit abnormal complement biomarkers and C3 deposition in a subset of patients and fall under the umbrella of “C3 dominant glomerulonephritis” [3]. Differentiating PIGN and C3GN can be challenging and largely dependent on the patient’s clinical and serological course. In our patient, PIGN was excluded based on symptomatology lasting longer than 8–12 weeks, with no evidence of any preceding infection. Paraprotein-associated glomerulonephritis was excluded as it typically presents in adults age >50 years and rarely in children, and there was no histopathology or immunofluorescence evidence of paraprotein mediated processes in the kidney biopsy. As such, no further workup for monoclonal gammopathy was warranted. In all cases of suspected C3GN, renal biopsy is required to establish the diagnosis and samples must show glomerular C3 staining. Immunofluorescence-based classification subdivides MPGN based on the composition of the glomerular deposits with either isolated or combined immunoglobulin or C3 molecules, and the lack of immunoglobulin deposition on immunofluorescence excluded autoimmune type immune complex-mediated MPGN.

Definitive treatment for C3GN has not yet been established, largely due to the rarity of the disease and the lack of randomized controlled trials to guide therapies. A number of treatments have been proposed, including antiproteinuric medications (ACE inhibitors), corticosteroids, MMF, rituximab, calcineurin inhibitors, and complement inhibitors (eculizumab) [3]. Treatment with MMF + steroids has shown significant potential in retrospective studies to improve renal outcomes [6]. One recent retrospective, multicenter study comprising of 97 patients found that MMF + steroids were superior to both immunosuppressive (including corticosteroids alone, cyclophosphamide, azathioprine, tacrolimus, cyclosporine, and rituximab) and eculizumab in inducing remission and preventing kidney failure [7]. Although optimal treatment length with MMF has not been established, the study showed that longer treatment with MMF (>12 months) is associated with a lower risk of relapse [7]. This present case provides evidence of the full responsiveness of a rare form of complement dysregulation C3GN to ACEi plus a combination of MMF and corticosteroids therapy. Once steroid was tapered off, ACEi and MMF were continued for maintenance therapy and were sufficient to induce remission for >2.5 years after initial presentation.

C3GN is most commonly an acquired disorder; however, studies have shown that genetic mutations in complement-associated genes may be present in up to 25% of patients [8]. The clinical utility of gene screening for C3GN remains to be defined. It has been shown that while MMF + steroids may be beneficial for both genetic and autoimmune-mediated forms of the disease, patients with autoantibody-mediated forms may be more responsive to therapy and more likely to achieve complete remission. This may make MMF a particularly appealing option for patients with elevated autoantibodies such as C3NeF, as seen in the present case. The high levels of C3NeF in the present case favor an acquired etiology, and it is unclear whether genetic testing would have affected treatment.

Furthermore, our present case raises the possibility of an association between C3GN and autoimmune disease. Despite complete renal recovery with no clinical symptoms, the patient

continues to follow rheumatology for monitoring of possible ANA-Negative Lupus and was maintained on a course of hydroxychloroquine 200 mg daily for 18 months following initial rheumatological evaluation. Lupus with negative ANA presents in about 10% of all lupus cases, and our patient does not fit 4 of the 11 American College of Rheumatology criteria for lupus. It has been suggested that an autoimmune milieu may serve as a trigger for the development of C3GN [9]. SLE has been associated with C3GN and lipodystrophy in several case studies [10]. In 1 cohort of 85 patients diagnosed with C3GN, 10/85 patients had coexisting autoimmune disease which usually arose early in the C3GN course. Patients were treated with immunosuppressive therapy and exhibited excellent response, suggesting the presence of autoimmune disease may portend a better prognostic course for C3GN [11]. Our case further highlights this potential association and the possible benefits of recognizing and treating these conditions concurrently.

### Statement of Ethics

The family of the patient gave written informed consent for publication of this case report including publication of images. This case study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The article is exempt from Ethical Committee approval as a single case is not required for approval.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

Rabbeh Aziz contributed to the diagnosis and treatment. Rong Deng contributed to writing of the manuscript. Lin Liu contributed to the pathological diagnosis. Shauna Tarsi contributed to clinical practice and patient care. Wayne R. Waz contributed to clinical practice and patient care. Xiaoyan Wu contributed to initial diagnosis, data analysis, editing of the manuscript, and submission. She is the corresponding author: xwu@upa.chob.edu. All the authors reviewed and approved the final version of the manuscript.

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