

## C3 Glomerulonephritis: A Rare Etiology of the Pulmonary Renal Syndrome



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C3 Glomerulopathy is a rare form of kidney disease due to dysregulation of the alternative complement pathway. We report a case of a college-aged woman with C3 glomerulonephritis (C3GN), presenting with the unexpected extrarenal manifestation of pulmonary hemorrhage. The patient presented with a nephritic urinary sediment and acute kidney injury after a recent infection. Kidney biopsy demonstrated focal endocapillary proliferative, crescentic, and necrotizing glomerulonephritis with bright glomerular C3 staining only. Electron microscopy revealed mesangial, intramembranous, and subendothelial deposits. After 2 doses of intravenous methylprednisolone, the patient developed spontaneous hemoptysis and respiratory compromise requiring emergent intubation. Bronchoscopy and computed tomography findings were consistent with diffuse alveolar hemorrhage. Notable laboratory results included C3, 40 (reference range, 75-175) mg/dL, and negative antinuclear antibody, antineutrophil cytoplasmic antibody, and anti-glomerular basement membrane serology results. As an outpatient, genetic testing revealed the presence of C3 glomerulopathy risk alleles. A diagnosis of C3GN complicated by pulmonary hemorrhage was made. There was initial response to treatment with steroids and mycophenolate mofetil; however, after repeated relapses of proteinuria and hematuria, treatment with eculizumab showed an initial response, but the patient subsequently became hemodialysis dependent. Our case highlights that C3GN can present with crescents and have other extrarenal manifestations such as pulmonary hemorrhage and should also be considered part of the differential diagnosis in patients presenting with pulmonary renal syndrome.

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*Kidney Med.* 1(1):36-39.  
Published online January 14, 2019.

doi: [10.1016/j.xkme.2018.12.002](https://doi.org/10.1016/j.xkme.2018.12.002)

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### INTRODUCTION

C3 Glomerulopathy (C3G) is a rare form of kidney disease due to dysregulation of the alternative complement pathway.<sup>1</sup> The pathologic hallmark of C3G lies in immunofluorescence findings of bright staining along the glomerular capillary walls for C3 with the absence of other findings. Two distinct entities exist in the form of C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), which are differentiated based on electron microscopy findings.<sup>2,3</sup> Major causes or triggers of C3G include infection, monoclonal gammopathy, autoimmunity, and genetic factors.<sup>4</sup>

Initially thought to be a renal-confined condition, C3G is also known to have extrarenal manifestations primarily in the form of ocular drusen in both forms of C3G.<sup>5</sup> Recently, a case of DDD with pulmonary involvement was reported.<sup>6</sup> We now report a case of biopsy-proven C3GN presenting with pulmonary hemorrhage. This case adds further evidence to the need for C3G to be considered in the differential diagnosis of pulmonary renal syndrome.

### CASE REPORT

A college-aged woman presented to the emergency department with flank pain and hematuria. Approximately 8 weeks before, she had polyarthralgia and a purpuric rash over the abdomen, buttocks, and lower extremities with associated edema. She was initially treated for possible streptococcal pharyngitis infection in the setting of a high anti-streptolysin O titer (1,490 IU/mL) with oral antibiotics at that time.

On examination, blood pressure was 126/70 mm Hg, heart rate was 76 beats/min, and oxygenation was 98% while breathing room air. The patient demonstrated persistent petechial rash and new right-sided costovertebral angle tenderness, with absence of fever or pulmonary symptoms on presentation. Laboratory evaluation showed the following values: hemoglobin, 8.1 g/dL; creatinine, 1.6 mg/dL; protein excretion of 4.9 g predicted 24-hour proteinuria; and dysmorphic hematuria, with more than 100 red blood cells per high-power field (Table 1).

Kidney biopsy was performed and showed focal endocapillary proliferative, crescentic, and necrotizing glomerulonephritis. Five of 22 glomeruli demonstrated crescents. There was no interstitial fibrosis or tubular atrophy present. On immunofluorescence, there was bright glomerular C3 staining and negative staining for immunoglobulin A (IgA), IgG, IgM, C1q, and  $\kappa$  and  $\lambda$  light chains (Fig 1). Pronase digestion was performed and did not show masked immunoglobulins. On electron microscopy there were mesangial, intramembranous, and subendothelial deposits with absence of subepithelial humps (Fig 2). A diagnosis of C3GN with crescents and an endocapillary proliferative pattern of injury was made.

Treatment was initiated with pulse dose intravenous methylprednisolone, 1 g. After the second dose, the patient developed spontaneous hemoptysis and ventilatory compromise requiring emergent intubation. Computed tomography of the chest showed dense airspace opacities throughout the left lung and scattered patchy airspace opacities throughout the right lung suggestive of diffuse alveolar hemorrhage. Bronchoscopy confirmed diffuse

**Table 1.** Key Laboratory Studies

Assay	Values	Reference Range
Hemoglobin, g/dL	8.1	12.0-15.5
White blood cell count, $\times 10^9/L$	5.6	3.5-10.5
Platelet count, $\times 10^9/L$	285	150-450
Serum total protein, g/dL	7.0	6.3-8.2
Serum albumin, g/dL	3.8	3.5-5.0
Serum creatinine, mg/dL	1.6	0.6-1.1
Estimated GFR (MDRD), mL/min/1.73 m <sup>2</sup>	41	>60
Total bilirubin, mg/dL	0.4	0.1-1.0
Aspartate aminotransferase, mg/dL	17	8-43
Alanine aminotransferase, mg/dL	22	10-43
HIV, HBsAg, anti-HCV	Negative	NA
SPEP, UPEP, IFE	Negative	NA
C3, mg/dL	40	75-175
C4, mg/dL	6	14-40
APFA, %	55%	75%-170% of normal
CFH autoantibody	Negative	Negative
C3 nephritic factor	Negative	Negative
sMAC, mg/L	0.20	<0.3
ANA, units	0.5	<1.0
PR3-ANCA, units	<0.2	<0.4
MPO-ANCA, units	<0.2	<0.4
Anti-GBM, units	<0.2	<1.0
ASO titer, IU/mL	1,490	0-530
Cryoglobulin	Negative	Negative

Note: Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; bilirubin in mg/dL to  $\mu\text{mol/L}$ ,  $\times 17.1$ ; serum urea nitrogen in mg/dL to mmol/L,  $\times 0.357$ .

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; APFA, alternate pathway functional assay; ASO, anti-streptolysin O; C, complement; CFB, complement factor B; CFH, complement factor H; GBM, glomerular basement membrane; GFR, glomerular filtration rate; HBsAg, hepatitis B surface antigen; HCV, hepatitis C; HIV, human immunodeficiency virus; IFE, immunofixation electrophoresis; MDRD, Modification of Diet in Renal Disease; MPO, myeloperoxidase; NA, not applicable; PR3, proteinase 3; sMAC, serum membrane attack complex; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

alveolar hemorrhage, and bronchoalveolar lavage cultures were negative for concomitant pulmonary infection. The patient was treated with 5 sessions of plasmapheresis and was transitioned to prednisone and mycophenolate mofetil treatment with improvement in her symptoms and kidney function.

Evaluation of the complement system showed C3 level of 40 mg/dL, and C4 level of 6 mg/dL, with decreased function of the alternate complement pathway at 55% (75%-170% normal range; Table 1). Genetic testing showed 5 copies of C3GN risk alleles (Table 2).

While on treatment with prednisone and mycophenolate mofetil, the patient developed progressive increases in proteinuria and declining kidney function. As a result, 2  $\frac{1}{2}$  years from the time of initial presentation, she was started on eculizumab therapy at 900 mg intravenously weekly for 4 weeks, with subsequent dose increases to 1,200 mg every 2 weeks with a good initial response,

documented by inactive urinary sediment with an improvement in proteinuria and creatinine level. However, 6 months after the initial response to eculizumab treatment, she continued to have relapses of worsening proteinuria, active urinary sediment, and a progressive decline in kidney function. She completed 8 months of treatment with eculizumab, which she tolerated well. Despite retreatment with 1 g of intravenous methylprednisolone and maintenance prednisone therapy, her kidney function continued to deteriorate. Approximately 12 months after initiation of eculizumab treatment, the patient progressed to end-stage kidney disease and was started on hemodialysis therapy.

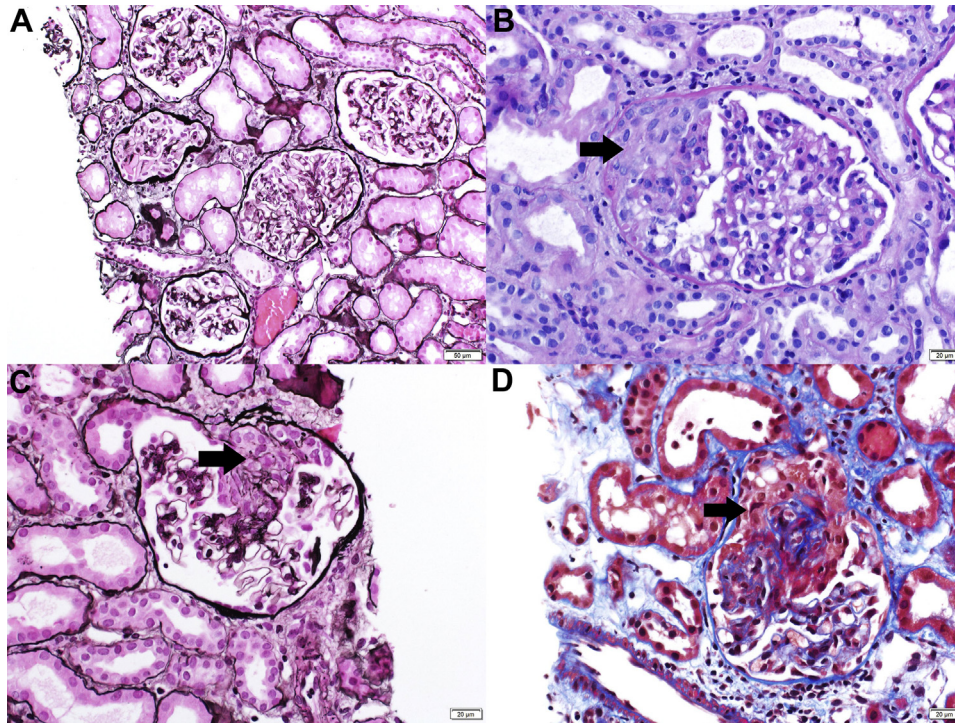
## DISCUSSION

We report a case of a young woman with C3GN associated with the unexpected extrarenal manifestation of pulmonary hemorrhage. Along with a recent case report of pulmonary-renal involvement of DDD, we believe this is the first report of C3GN-associated pulmonary renal syndrome. This is not surprising because both DDD and C3GN share the same pathogenic process.

C3G is a disease entity that has been identified in patients with acquired abnormalities or genetic mutations, including those to complement factor H, which was identified in this patient.<sup>3,7,8</sup> These abnormalities provide the basis for the alternative complement pathway to become dysregulated, resulting in uncontrolled activation of the complement cascade, with glomerular deposition of complement factors and degradation products, leading to glomerular injury and inflammation.

C3G can present as crescentic glomerulonephritis similar to antineutrophil cytoplasmic antibody vasculitis. However, C3G presenting as pulmonary renal syndrome is unusual. Currently the only major extrarenal finding in patients with C3G is ocular drusen.<sup>5</sup> There has only been 1 additional report of C3G-related pulmonary involvement in a case of a patient with DDD.<sup>6</sup> With glomerular disease related to the deposition of complement factors along the glomerular basement membrane, we postulate that a similar mechanism of damage may occur in the highly vascular pulmonary capillary basement membrane network. However, it is unclear why clinical manifestations of pulmonary involvement are rare in patients with C3G.

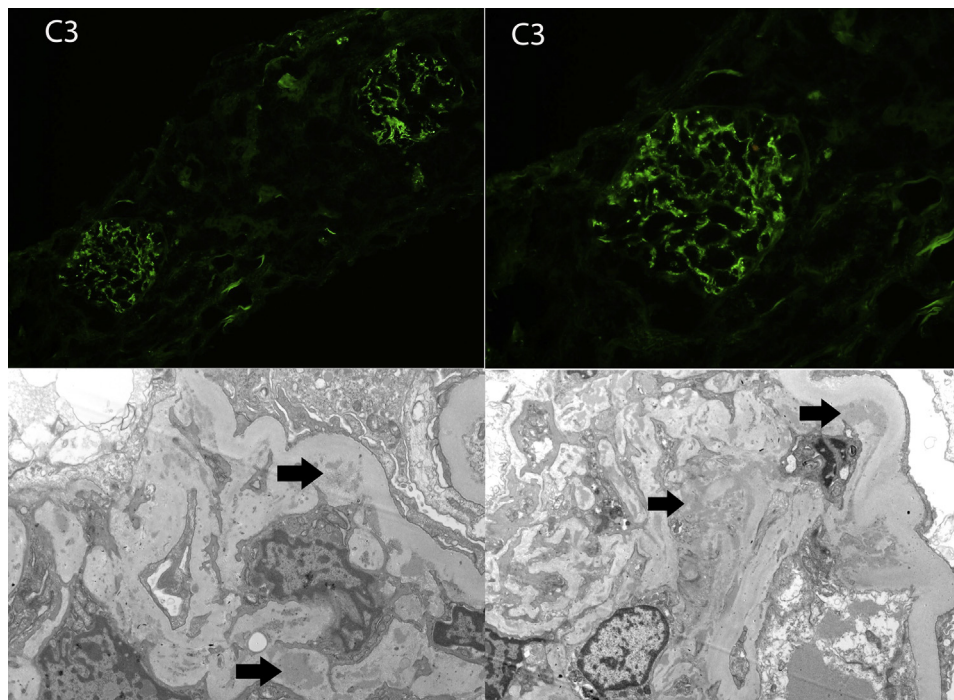
Another key factor in this case was the triggering event. Our recent series describing a 10-year experience on C3G shows that infection plays a major role as a trigger. Thirty-three of 114 (28.9%) cases presented after an infection, with 3 of the 33 having positive anti-streptolysin O titers, similar to our patient. Infection can activate the alternative complement pathway and uncover a genetic predisposition to C3GN.<sup>3</sup> Of the other triggers, our patient had no evidence of monoclonal gammopathy and no autoimmunity or C3 nephritic factor, but had risk alleles identified on genetic testing (Table 2).



**Figure 1.** Light microscopy findings. (A) Periodic acid–Schiff (PAS) stain shows normal glomeruli. (B) Hematoxylin and eosin stain, (C) PAS stain, and (D) Masson trichrome stain each show cellular crescents (arrows) and endocapillary proliferation.

We acknowledge that in the presence of antecedent infection, it may be difficult to distinguish this case of C3GN from that of infection-related glomerulonephritis. From a pathology standpoint, there was bright staining for C3 in the

mesangium and capillary wall on immunofluorescence, with the absence of immunoglobulin on pronase testing.<sup>9</sup> On electron microscopy, there were intramembranous and subendothelial deposits with the absence of subepithelial



**Figure 2.** (Upper panel) Immunofluorescence shows bright staining for C3 in the mesangium and capillary wall. (Lower panel) Electron microscopy findings show intramembranous, subendothelial, and mesangial electron-dense deposits.



**Table 2.** DDD/C3GN-Associated Risk Variants Identified in This Patient

Gene	Risk Allele	Nucleotide	Patient No. of Copies
CFH	p.Val62	c.184G	2
CFH	p.His402	c.1204C	1
C3	p.Gly102	c.304G	1
C3	p.Leu314	c.941T	1

Abbreviations: C, complement; C3GN, C3 glomerulonephritis; CFH, complement factor H; DDD, dense deposit disease.

humps. Clinically, the persistence of active glomerulonephritis for many years following the initial presentation, as well as evidence of persistent alternative complement pathway dysfunction with genetic abnormalities, is in contrast with the clinical course of infection-related glomerulonephritis.<sup>10</sup> Taken together, these findings help differentiate this case of C3GN from infection-related glomerulonephritis as reported in our prior series.<sup>9</sup>

From an outcome perspective, our patient was initially treated similarly to a patient with pulmonary renal syndrome, with pulse dose steroids and plasmapheresis with good initial response. Treatment was then maintained with low-dose prednisone and mycophenolate mofetil, but the disease progressed despite the addition of eculizumab, with the patient developing end-stage kidney disease 3 1/2 years after the initial diagnosis. Our recent case series highlighted that of patients with C3GN treated with various forms of immunosuppression; ~25% of patients progressed to end-stage kidney disease after almost 2 years from diagnosis, suggesting a variable but often poor outcome in these patients.<sup>4</sup>

In conclusion, our case highlights that C3GN can present with crescents and have other extrarenal manifestations such as pulmonary hemorrhage and should also be considered part of the differential diagnosis in patients presenting with pulmonary renal syndrome.

## ARTICLE INFORMATION

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**Support:** None.

**Financial Disclosure:** The authors declare that they have no relevant financial interests.

**Peer Review:** Received November 16, 2018. Evaluated by 1 external peer reviewer, with direct editorial input from the Editor-in-Chief. Accepted in revised form December 24, 2018.

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