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Acute Kidney Injury Due to Collapsing Glomerulopathy Following COVID-19 Infection

Yonatan Peleg[1], Satoru Kudose[2], Vivette D'Agati[2], Eric Siddall[1], Syeda Ahmad[1], Thomas Nickolas[1], Sergey Kisselev[1], Ali Gharavi[1] and Pietro Canetta[1]

[1]Department of Medicine, Division of Nephrology, Columbia University Irving Medical Center, New York, New York, USA; and [2]Department of Pathology, Division of Renal Pathology, Columbia University Irving Medical Center, New York, New York, USA

Correspondence: Pietro Canetta, Department of Medicine, Division of Nephrology, Columbia University Irving Medical Center, 622 W. 168th Street, PH4–124, New York, New York 10032, USA. E-mail: Pac2004@cumc.columbia.edu

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INTRODUCTION

A 46-year-old West African man presented to our hospital's emergency room on March 15, 2020, with severe acute kidney injury. He reported that 2 to 3 weeks before his hospital presentation he had had subjective fever, myalgias, sore throat, and cough, which he had treated with multiple doses of ibuprofen. These complaints resolved 1 week before this hospital presentation, but he subsequently developed worsening abdominal pain, nausea, and anorexia that persisted for the following week, leading to his hospital presentation. He described lightheadedness when rising from a recumbent position. He reported decreased urine output but denied gross hematuria, frothy urine, or flank pain. He denied any new lower extremity edema or orthopnea, vomiting, diarrhea, change in mentation, persistent respiratory infectious symptoms, recent travel, or sick contacts. Other than his recent use of ibuprofen, he denied any other medication, vitamin supplementation, or herbal remedy. His medical history included obesity and obstructive sleep apnea for which he used nocturnal continuous positive airway pressure therapy. Baseline serum creatinine was 1.1 mg/dl (estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation, 93 ml/min per 1.73 m^2) on routine laboratory testing 16 months prior. He had no family history of kidney disease. He was born in Nigeria, worked as a nurse, lived with his wife and children in New York City, and did not use tobacco or illicit drugs.

CASE PRESENTATION

On initial presentation, vital signs were notable for blood pressure 144/100 mm Hg, heart rate 76 beats per minute, respiratory rate 16 breaths per minute, and SpO2 94% breathing ambient air while lying flat in bed. Body mass index was 44 kg/m^2. He had mild tenderness to palpation in the epigastrium and periumbilical region and trace lower extremity edema; the remainder of the examination was unremarkable. Laboratory tests were notable for severe acute kidney injury (presenting serum creatinine, 12.5 mg/dl) with nephrotic range proteinuria, hypoalbuminemia, elevated lactate dehydrogenase, and elevated inflammatory markers. Initial laboratory assessment and selected trends are shown in Table 1. Imaging studies included a chest X-ray showing mild pulmonary vascular congestion, a renal ultrasound with Doppler showing a 14.3 cm right kidney and 14.1 cm left kidney with bilaterally increased echogenicity and normal arterial and venous Doppler flow, a computed tomography scan of the abdomen and pelvis without iodinated contrast showing mild hepatic steatosis and normal-sized spleen, and a nuclear renal scan with dimercaptosuccinic acid showing equal perfusion to both kidneys without cortical defects.

The patient was initially treated with several liters of isotonic fluid; however, his kidney function did not improve and he remained oliguric with orthopnea and persistent nausea. Therefore, a tunneled dialysis catheter was placed and he began intermittent hemodialysis on hospital day 4. Serologic screens were negative for HIV antibody, hepatitis C antibody, hepatitis B surface antigen and core antibody, anti-nuclear antibody, anti-

Table 1. Summary of laboratory evaluations and relevant trends during hospitalization

		Hospital Day										
Measure	**Reference**	**1**	**2**	**3**	**4[a]**	**6**	**9**	**10**	**11**	**13**	**16**	**17**
Sodium (mmol/l)	137–145	132	131	129	134							
Potassium (mmol/l)	3.5–5.1	3.6	3.5	3.9	4.1							
Chloride (mmol/l)	98–107	86	85	85	84							
Carbon dioxide (mmol/l)	19–27	19	15	15	12							
Blood urea nitrogen (mg/dl)	7.0–26	69	96	110	135							
Creatinine (mg/dl)	0.7–1.3	12.5	15	16.8	19.9							
Glucose (mg/dl)	75–100	100	87	101	42							
Calcium (mg/dl)	8.8–10.3	7.2	6.4	6.7	6.5							
Albumin (g/dl)	3.9–5.2	3.1	2.5	2.1	2.9	3.1	3.1	3.2	3.3	3.2	3.7	3.6
Triglycerides (mg/dl)	<149		422									
Total cholesterol (mg/dl)	<200–239		179									
Hemoglobin A1c (%)	<5.7	7.1										
White blood cell count (10^3 per μl)	3.12–8.44	7.7	6.1	7.7	6.6							
Absolute lymphocyte count (per μl)	1000–3900	1690										
Hemoglobin (g/dl)	12.6–17	16.6	14.5	15.2	14.2							
Platelets (10^3 per μl)	156–325	242	282	349	394							
Urine protein:creatinine ratio (g/g)	<0.15	3.021				5.805						
24-h urine protein excretion (g/24 h)	<0.15									10.376		
Urine RBC (per hpf)	0–2	2										
Lactate dehydrogenase (U/l)	135–255		1504		1561				1258	943	828	972
Creatine kinase (U/l)	64–499		1628	1163	873	547	227					
Erythrocyte sedimentation rate (mm/h)	0–15		>130						119			
High-sensitivity C-reactive protein (mg/l)	0–10		49.4						36.3			
Ferritin (ng/ml)	30–400	1147							500.7			
Interleukin-6 (pg/ml)	≤5								12			
Interleukin 2 receptor (pg/ml)	<1033							1530				
Sars-CoV-2 RT-PCR	Not detected							Detected			Not detected	Detected

Hpf, high-power field; RBC, red blood cell; RT-PCR, reverse-transcriptase polymerase chain reaction.
[a]Dialysis initiated on hospital day 4.

DNA antibody, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, and cryoglobulin. Serum and urine protein electrophoresis and immunofixation were negative for monoclonal protein, and the kappa/lambda free light chain ratio was normal. The patient remained afebrile throughout his hospital course, and after several dialysis sessions his orthopnea improved and he was normoxemic breathing ambient air. A kidney biopsy was performed on hospital day 9.

Pathology

The biopsy contained 2 cores of renal cortex. There were 20 glomeruli, none of which were globally sclerotic. Fourteen glomeruli demonstrated segmental to global collapse of the glomerular capillaries accompanied by exuberant hypertrophy and hyperplasia of the overlying glomerular epithelial cells, some of which contained prominent protein droplets positive for periodic acid–Schiff. The 6 uninvolved glomeruli appeared normal in size and cellularity. No inflammatory crescents, ruptures of Bowman's capsule, or fibrinoid necrosis were identified (Figure 1). The cortex also demonstrated diffuse and severe tubular degenerative and regenerative changes characterized by epithelial simplification, loss of brush border, enlarged nuclei with prominent nucleoli, and focal mitotic figures. Some proximal tubular cells contained abundant intracytoplasmic protein droplets positive for periodic acid–Schiff. Scattered tubular microcysts were seen. The interstitium was expanded by edema and mild to moderate interstitial inflammation, composed predominantly of mononuclear leukocytes and occasional plasma cells, without tubulitis. There was mild focal tubular atrophy and interstitial fibrosis involving approximately 10% of the cortical parenchyma. Vessels demonstrated minimal arteriosclerosis and mild to moderate arteriolosclerosis.

Immunofluorescence performed on 2 glomeruli showed no specific immune staining for IgG, IgM, IgA, C3, C1q, kappa, or lambda involving the glomeruli. Proximal tubular cells contained protein droplets staining for albumin. The tissue submitted for electron microscopy contained no glomeruli. Cortical tubules showed acute epithelial injury and protein resorption droplets. No virions were detected by electron microscopy in tubular cells. The biopsy findings were interpreted as consistent with the collapsing variant of focal segmental glomerulosclerosis (FSGS), also known as collapsing glomerulopathy (CG).

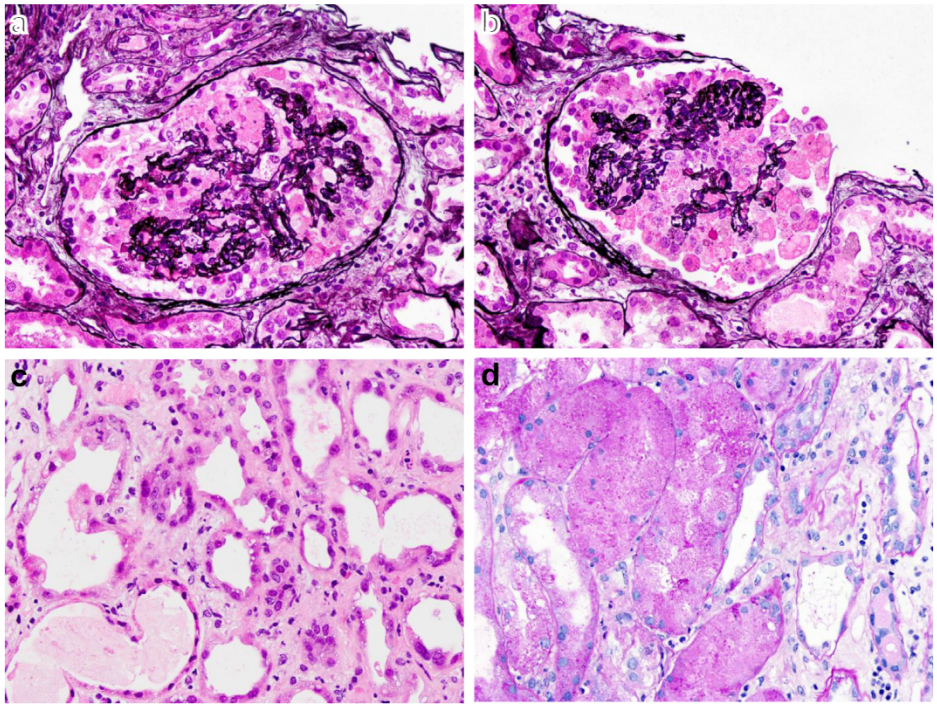

Figure 1. Renal biopsy. Representative light microscopy demonstrates global collapse of the glomerular capillary loops accompanied by hyperplasia of overlying glomerular epithelial cells, many of which contain abundant eosinophilic intracytoplasmic protein droplets (a,b, Jones methenamine silver stain, original magnification ×400). Acute tubular injury involves many cortical tubules, accompanied by interstitial edema and mild interstitial mononuclear inflammatory infiltrates (c, hematoxylin-eosin stain, original magnification ×400). Scattered proximal tubules contain abundant intracytoplasmic periodic acid–Schiff–positive protein resorption droplets (d, periodic acid–Schiff stain, original magnification ×400).

Clinical Course

After the biopsy result, serum viral polymerase chain reactions were obtained and resulted negative for HIV-1 RNA, parvovirus B19 DNA, Epstein-Barr virus DNA, cytomegalovirus DNA, and adenovirus DNA. Repeat chest X-ray on hospital day 10 showed improvement in pulmonary vascular congestion and no new pulmonary infiltrate. Nevertheless, given the biopsy findings and his recent resolved respiratory illness, on hospital day 10, he was screened for coronavirus disease 2019 (COVID-19) by nasal swab and was found to be positive for the severe acute respiratory syndrome–novel Coronavirus 2 (SARS-CoV-2) by reverse-transcriptase polymerase chain reaction.

Because he lacked respiratory symptoms, the infectious disease service deemed him not to be a candidate for clinical trial of remdesivir. A request for tocilizumab was initially declined because it was in short supply and reserved for life-threatening respiratory failure. As shown in Table 1, despite an interim negative screen, he continued to screen positive for SARS-CoV-2 on hospital day 17. Although his lactate dehydrogenase down-trended and albumin up-trended toward the end of his hospitalization, he remained dialysis dependent. On hospital day 23, tocilizumab became available and he was dosed 400 mg. He was also started on prednisone 80 mg daily with a plan for 1 month of therapy with further taper to be determined based on change in residual renal function. He remained dialysis dependent at the time of this report (hospital day 26), with predialysis serum creatinine of 16.6 mg/dl.

Additional Studies

Written informed consent was obtained from the patient for genotyping for the *Apolipoprotein 1* (*APOL1*) G1 and G2 alleles, which was performed by Sanger sequencing from genomic DNA extracted from paraffin-embedded biopsy tissue. This revealed the patient to be homozygous for the G1 allele (Supplementary Material, Supplementary Figure S1). *In situ* hybridization for SARS-CoV-2 performed on formalin-fixed paraffin-embedded kidney tissue sections using an RNA probe to the receptor binding domain of the spike protein was negative (Figure 2).

DISCUSSION

Here we present a 46-year-old West African man with severe acute kidney injury requiring renal replacement therapy due to CG in the context of COVID-19 illness. CG not associated with HIV/AIDS was first described in the mid-1980s in a small case series of African

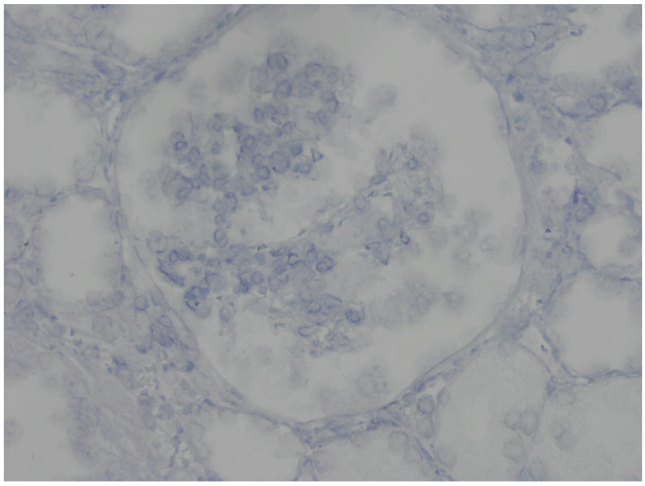

Figure 2. Severe acute respiratory syndrome–novel Coronavirus 2 (SARS-CoV-2) *in situ* hybridization. A representative glomerulus and the adjacent cortical tubular epithelial cells show negative staining for SARS-CoV-2 by *in situ* hybridization (original magnification ×400).

American patients with nephrotic syndrome and rapidly progressive irreversible kidney failure.[1] CG is an aggressive variant of FSGS exhibiting high rates of podocyte injury and depletion. Light microscopy is typified by hyperplastic and hypertrophic visceral epithelial cells overlying segmentally or globally collapsed glomerular capillaries that are narrowed or obliterated by wrinkling and retraction of glomerular basement membranes. At the ultrastructural level, podocytes show severe foot process effacement with focal podocyte detachment and parietal cell coverage. Cases associated with viral infection, such as HIV, may have endothelial tubuloreticular inclusions (interferon footprints). The tubulointerstitial compartment often contains an infiltrate of mononuclear cells, including monocytes, CD4+ and CD8+ T cells, and variable plasma cells. Tubular epithelial cells typically display degenerative and regenerative changes and aberrant cellular proliferation and differentiation, leading to microcystic transformation. Tubular atrophy and interstitial fibrosis are common; however, comparative studies have shown that these indices were numerically but not significantly more frequent in CG compared with noncollapsing FSGS.[2] A dysregulated podocyte phenotype has been identified in both HIV and non–HIV-associated CG. As podocytes are injured and depleted, the visceral epithelial cells show down-regulation and loss of mature podocyte markers with *de novo* expression of markers associated with proliferation and activated parietal epithelial cells.[3,4]

CG not associated with HIV/AIDS may be idiopathic or associated with a variety of conditions, including other viral infections (such as Epstein-Barr virus, influenza, cytomegalovirus, and parvovirus B19) and nonviral infections (such as tuberculosis), autoimmune diseases (such as systemic lupus erythematosus), drug exposures (such as pamidronate and interferon), hemophagocytic syndrome, and acute glomerular ischemia, among others.[5] Many of these exposures are thought to mediate CG by podocyte cytotoxicity, such as via proinflammatory cytokine expression including type 1 interferons.[6] It is also well recognized that a large proportion of patients with CG carry 2 allelic risk variants of *APOL1*, namely G1 and G2, which are common in individuals of West African ancestry and also confer risk for hypertension-attributed end-stage kidney disease.[7] Indeed, the *APOL1* high-risk genotype (either G1/G1, G1/G2, or G2/G2), which is found in approximately 10% to 15% of the African American population, is disproportionately represented in patients with HIV-associated nephropathy and non–HIV-associated CG. In general, patients with 2 high-risk *APOL1* alleles have a higher likelihood of eventually reaching end-stage kidney disease, although their response to immunosuppression is not modified by their *APOL1* high-risk status.[8] Evidence from animal models and cell culture systems suggests that the high-risk *APOL1* genotype may mediate podocyte damage via upregulation of APOL1 through activation of a viral program in the podocyte, leading to dysregulated endosomal trafficking and autophagic flux, resulting in podocyte depletion and glomerular scarring.[6] With the exception of HIV-associated nephropathy and parvovirus B19–associated CG, in which virus has been identified in renal epithelial cells, other virally mediated forms of CG in patients with high-risk *APOL1* genotype typically lack evidence of direct viral infection of the renal parenchyma, supporting potential interferon-mediated podocyte effects. In our case, *in situ* hybridization did not detect SARS-CoV-2 in the renal tissue.

Long-term renal prognosis in patients with CG not related to HIV/AIDS is guarded. Valeri and colleagues[2] reported a mean time from biopsy to end-stage kidney disease to be 13 months in 43 cases of idiopathic CG (average creatinine at baseline, 4.2 mg/dl) compared with 62.5 months in 50 age-matched controls with FSGS not otherwise specified (average creatinine at baseline, 2.0 mg/dl). Moreover, none of the patients with CG in this series achieved remission with glucocorticoid therapy, although 3 of 43 had a spontaneous remission and 2 of 5 patients treated with cyclosporine achieved a remission.[2] Another series compared outcomes between 61 patients with CG (average creatinine at baseline, 1.5 mg/dl) and 126 patients with FSGS not otherwise specified (average creatinine at baseline, 1.2 mg/dl) and found that, overall, 48% of patients with CG versus 26% of patients with FSGS not otherwise specified reached

end-stage kidney disease at 69 months. However, the authors reported that among patients with CG who were immunosuppressed (with steroids, calcineurin inhibitors, or both), 70% achieved remission.[9]

Generally, patients with idiopathic CG without severe glomerulosclerosis or interstitial fibrosis are offered immunosuppression with steroids or calcineurin inhibitors based on evidence that immunosuppression may improve remission rates and that high-risk *APOL1* genotype status does not modify response to immunosuppression.[8,9] It is less clear, however, whether patients who develop CG related to a viral illness (such as cytomegalovirus, adenovirus, parvovirus B19, and Epstein-Barr virus, among others) should also receive immunosuppression. There are reports of treating patients with CG related to cytomegalovirus viremia simultaneously with antiviral therapy and glucocorticoids with good effect.[S1,S2]

In December 2019, COVID-19 emerged in Wuhan, China, and has rapidly become a global pandemic.[S3] Severe disease is typified by a cytokine release syndrome with increased levels of IL-6, IL-10, IL-2, and interferon-gamma, as well as increased proliferation of the Th17 cell population.[S4] A recent prospective cohort study[S5] reviewed kidney disease among 701 patients who were treated for COVID-19 in Wuhan, China. Those patients with kidney disease had higher in-hospital mortality; moreover, there was evidence of hematuria in 26.7% and proteinuria in 43.9% of patients in their cohort. Although kidney tissue was not examined, the authors postulated potential multifactorial renal injury, including direct cytopathic effects (via viral entry through angiotensin-converting enzyme 2 receptors expressed on tubular epithelium), as well as tubular injury from cytokine storm, shock, and rhabdomyolysis.[S5] A recent publication of kidney findings at autopsy among 26 patients from China who died of severe respiratory failure from COVID-19 disease revealed that the predominant findings were acute tubular injury, erythrocyte aggregation in peritubular capillaries, and direct viral infection of tubular epithelium and podocytes; none had CG, although 2 had FSGS, but the morphologic variant of FSGS was not specified.[S6] The heightened cytokine release associated with COVID-19 infection places patients with the APOL1 high-risk genotype particularly at risk for interferon-mediated podocyte injury, as can occur in other virally mediated forms of CG, interferon therapy–induced CG, and lupus-associated CG. Patients with COVID-19 may have a biphasic disease course whereby after an initial onset of symptoms there is a time lapse (~8 days) of worsening respiratory symptoms that corresponds with an exuberant inflammatory response.[S3] In our patient with APOL1 high-risk genotype, it is plausible that an exuberant inflammatory response induced CG without the usual predominant pulmonary manifestations.

Table 2. Key teaching points

1. Collapsing glomerulopathy can be a presentation of COVID-19 even in the absence of severe respiratory disease.
2. Collapsing glomerulopathy should be suspected as a cause of acute kidney injury associated with proteinuria.
3. A high-risk Apolipoprotein 1 genotype, most commonly seen in individuals of sub-Saharan African ancestry, increases the pretest probability of collapsing glomerulopathy.
4. We did not detect severe acute respiratory syndrome–novel Coronavirus 2 in the renal tissue by *in situ* hybridization, suggesting that the collapsing glomerulopathy is a consequence of the hyperinflammatory phenotype of COVID-19 rather than direct viral infection of renal cells.
5. Treatment is uncertain; extrapolating from other forms of virus-associated collapsing glomerulopathy, there may be utility in glucocorticoids and/or antiviral medication.

COVID-19, coronavirus disease 2019.

CONCLUSION

idemic's spread to New York City. Larsen and colleagues[S7] reported another patient with CG associated with COVID-19 with more significant pulmonary manifestations. CG has not been reported in outbreaks in China and Europe, probably because *APOL1* high-risk genotypes are present only in populations of African ancestry. High-risk genotypes have been reported in 10% to 15% of African American individuals and can also be detected in persons of Hispanic/Afro-Caribbean ancestry. Considering the projected 50% to 80% attack rates of COVID-19 in the general population,[S8,S9] a significant fraction of the population with West African ancestry may be at risk of developing kidney injury from CG as the COVID-19 pandemic sweeps through the Americas and the African continent. As we learn more about the renal manifestations of COVID-19, we should keep in mind the possibility of CG among patients with COVID-19 with proteinuria and acute kidney injury, even among those with mild respiratory disease. Future research will be needed to determine optimal management, and particularly whether there is a role for antiviral and anti-inflammatory therapies, including nonspecific agents like glucocorticoids or targeted therapies against specific cytokines or leukocyte subsets (Table 2).

DISCLOSURE

All the authors declared no competing interests.

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for performing the *in situ* hybridization testing. This case report was approved by Columbia University Irving Medical Center IRB-AAAT0009 and IRB-AAAC7385.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

APOL1 Genotyping Methods.

Figure S1. Chromatogram of rs73885319 and rs60910145 sequence, representing the linked missense variants for the *APOL1* G1 risk allele, and rs71785313 sequence, representing the 6 base pair deletion for the *APOL1* G2 risk allele. The patient is homozygous for the G1 allele.

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