Kidney Medicine

COVID-19–Associated Collapsing Focal Segmental Glomerulosclerosis: A Report of 2 Cases

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Collapsing glomerulopathy is an aggressive form of focal segmental glomerulosclerosis with diverse causes. The presence of the apolipoprotein L1 (*APOL1*) high-risk genotype is a major risk factor for collapsing glomerulopathy in African Americans. Coronavirus disease 2019 (COVID-19) is an emerging pandemic with predominant respiratory manifestations. However, kidney involvement is being frequently noted and is associated with higher mortality. Currently, kidney pathology data for COVID-19 are scant and mostly come from postmortem findings. We report 2 African American patients who developed acute kidney injury and proteinuria in temporal association with COVID-19 infection. Kidney biopsy specimens showed collapsing glomerulopathy, endothelial tubuloreticular inclusions, and acute tubular injury, without evidence by electron microscopy or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in situ hybridization of viral infection of kidney cells. Both patients had the *APOL1* high-risk genotype. We propose that collapsing glomerulopathy represents a novel manifestation of COVID-19 infection, especially in people of African descent with *APOL1* risk alleles.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the initial disease presentation was predominantly respiratory illness, more data are now emerging for other potential organ injury, including kidney, gastrointestinal tract, blood, and heart.[1] Kidney involvement is frequent in patients with COVID-19 infection and is associated with higher mortality.[2] Very little is currently known regarding kidney pathology, with most information coming from autopsy studies from China suggesting acute tubular injury as the main pathology.[3,4] We describe 2 African American patients with COVID-19 infection who presented with acute kidney injury and proteinuria. Kidney biopsy specimens demonstrated acute tubular injury and collapsing glomerulopathy.

CASE REPORTS

Case 1

A 67-year-old African American woman with a medical history of hypertension, dyslipidemia, obstructive sleep apnea, gastroesophageal reflex, and type 2 diabetes mellitus presented to the hospital with malaise, poor appetite, nausea, vomiting, and abdominal pain for 2 weeks. On presentation, the patient had an elevated creatinine level at 2.2 mg/dL. One year prior, her baseline serum creatinine level was 1 mg/dL, and urinalysis showed trace blood and albumin-creatinine ratio of 22.8 mg/g.

Physical examination on presentation showed temperature of 100.2°F, blood pressure of 137/59 mm Hg, pulse rate of 85 beats/min, respiratory rate of 18 breaths/min, and oxygen saturation as measured by pulse oximetry of 97% while breathing room air. Examination was significant for dry oral mucosa, no peripheral edema, mild generalized abdominal tenderness, and diminished breath sounds at the right lung base.

Laboratory data on presentation (Tables S1 and S2) showed serum urea nitrogen level of 33 mg/dL and creatinine level of 2.2 mg/dL. Urinalysis showed 2 red blood cells/high-power field (HPF), 61 white blood cells/HPF, and proteinuria with protein excretion of 100 mg/dL. Urinary electrolytes showed fraction excretion of urea <35%. Spot urinary protein-creatinine ratio was 3,276 mg/g. Kidney ultrasound showed increased kidney echogenicity with no hydronephrosis. An x-ray of the chest showed subtle opacity in the right lateral base.

Treatment was initiated with intravenous hydration, ceftriaxone, and azithromycin. Home medication of lisinopril/hydrochlorothiazide was withheld. Nasopharyngeal swab for COVID-19 reverse transcriptase-polymerase chain reaction was positive. Urine culture was negative and antibiotic treatment was discontinued. The patient was started on treatment with hydroxychloroquine for 5 days and methylprednisolone, 40 mg, twice a day for 7 days. During hospitalization, she experienced no significant hypotension or respiratory distress. Despite hydration, there was a progressive decline in kidney function, with creatinine level of 8.27 mg/dL by day 8 of hospitalization, and dialysis was initiated.

Additional laboratory workup demonstrated negative results from human immunodeficiency virus (HIV) and hepatitis screens, complement C3 and C4 levels were within normal limits, and serologic tests, including antinuclear antibody, antineutrophil cytoplasmic antibody, and anti–glomerular basement membrane, were negative. Serum protein electrophoresis showed changes consistent

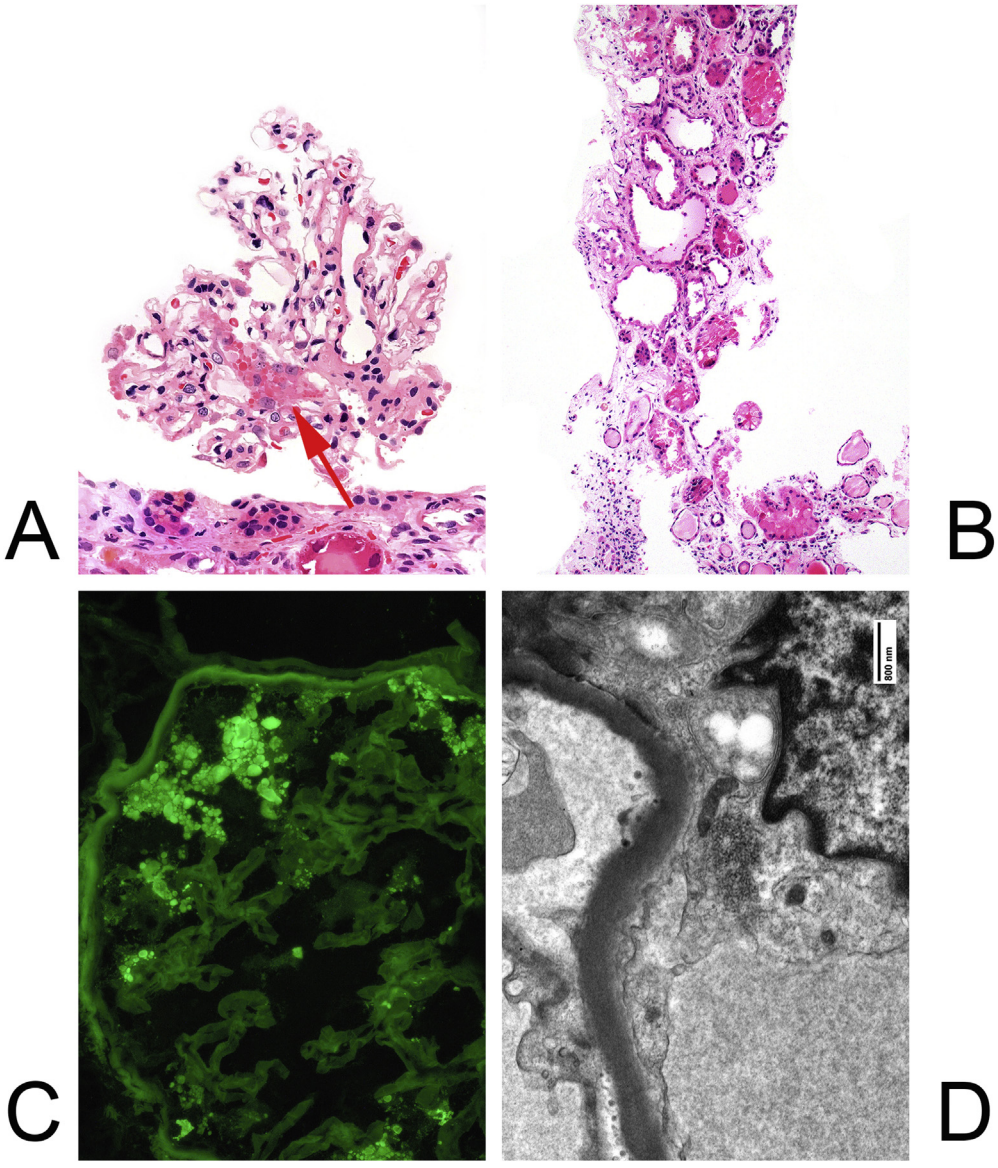

Figure 1. (A) Glomerular lesions in patient 1 included focal early collapsing lesions with numerous podocyte protein resorption droplets (arrow) (hematoxylin and eosin; original magnification ×400). (B) Acute tubular injury was prominent, evidenced by many dilated tubules with thinning of the epithelial lining (hematoxylin and eosin; original magnification ×100). (C) Direct immunofluorescence revealed no immune complex–type deposits but focal podocyte protein resorption droplets as illustrated in this stain for albumin (anti-albumin direct immunofluorescence; original magnification ×400). (D) Occasional tubuloreticular structures were identified in endothelial cells using electron microscopy (scale bar = 800 nm).

with an active inflammatory pattern and a normal polyclonal gamma globulin pattern. Urine protein electrophoresis showed a pattern consistent with mixed glomerular and tubular proteinuria. No monoclonal protein was noted on immunofixation.

Kidney biopsy demonstrated changes consistent with early collapsing glomerulopathy, including 2 glomeruli with segmental podocyte protein resorption droplets, collapse of the glomerular capillary tuft, focal glomerular erythrocyte congestion, diffuse acute tubular injury, and prominent tubular protein reabsorption droplets. Interstitial fibrosis and tubular atrophy were mild, with mild arterial intimal thickening and no significant hyaline arteriolosclerosis. Interstitial inflammation was minimal. Immunofluorescence was negative for immune deposits, and electron microscopy demonstrated extensive podocyte foot-process effacement with occasional endothelial tubuloreticular structures (Fig 1). No viral particles were identified in tubular cells or podocytes.

During the hospitalization, the patient experienced improvement in clinical symptoms and completed hydroxychloroquine and steroid therapy. At 8 weeks postbiopsy, she continues to require dialysis at an outpatient dialysis unit while being monitored for kidney recovery.

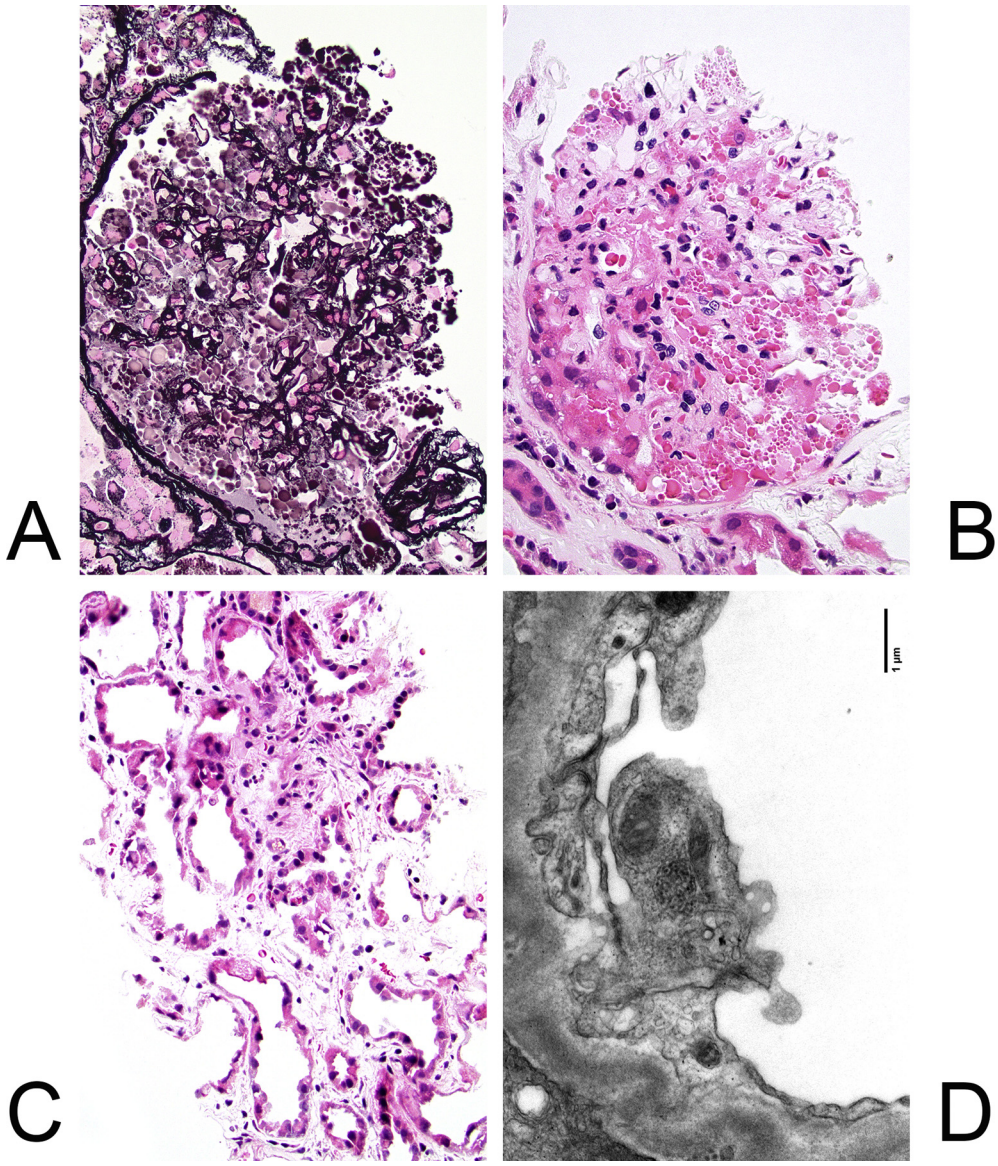

Figure 2. (A) Glomerular lesions in patient 2 included numerous collapsing lesions, illustrated on this silver stain with collapse of the glomerular capillary loops and increased extracapillary cellularity (Jones silver stain; original magnification ×400). (B) Numerous podocyte protein droplets were present circumferentially (hematoxylin and eosin; original magnification ×400). (C) Extensive tubular injury was also noted (hematoxylin and eosin; original magnification ×200). (D) Focal tubuloreticular structures were noted in endothelial cells using electron microscopy (scale bar = 1µm).

Case 2

A 49-year-old African American man with a medical history of hypertension, cardiomyopathy, peripheral vascular disease, and arthritis presented to the hospital with a 5-day history of loss of taste, nausea, and profuse vomiting and diarrhea associated with abdominal pain. Before presentation, he also had cough, shortness of breath, and low-grade fever for 2 days. Initial evaluation showed acute kidney injury with creatinine level of 4.85 mg/dL. One year prior, his baseline creatinine level was 0.95 mg/dL and baseline urinalysis showed negative blood and spot albumin-creatinine ratio of 25.7 mg/g. The patient was not taking any medications at home.

Physical examination on presentation showed temperature of 99.9°F, blood pressure of 144/86 mm Hg, pulse rate of 90 beats/min, respiratory rate of 18 breaths/min, and oxygen saturation as measured by pulse oximetry of 96% while breathing 4 L of oxygen through a nasal cannula. Examination was significant for dry oral mucosa, no peripheral edema, and lower abdominal tenderness. Bronchial breath sounds were present bilaterally.

Laboratory data on presentation (Tables S1 and S2) showed serum urea nitrogen level of 45 mg/dL and creatinine level of 4.85 mg/dL. Urinalysis showed 2 red blood cells/HPF and proteinuria with protein excretion > 500 mg/dL. Urine electrolytes showed fraction excretion

of sodium <1%. Spot urine protein-creatinine ratio was 2,598 mg/g. Kidney ultrasound showed increased kidney echogenicity with no hydronephrosis. An x-ray of the chest showed bilateral patchy and hazy airspace opacities.

Nasopharyngeal swab for COVID-19 reverse transcriptase-polymerase chain reaction came back positive. Treatment included intravenous hydration, hydroxychloroquine for 5 days, and methylprednisolone, 60 mg, twice daily for 7 days. The patient continued to have nausea, hiccups, and vomiting. Despite hydration, there was a progressive decline in kidney function, with creatinine level of 10.10 mg/dL by day 4 of hospitalization, and dialysis was initiated. Additional laboratory workup demonstrated negative HIV and hepatitis screen results, complement C3 and C4 levels within normal limits, and negative serologic test results including antinuclear antibody, antineutrophil cytoplasmic antibody, and anti–glomerular basement membrane. Serum protein electrophoresis was consistent with an active inflammatory pattern, without monoclonal protein on immunofixation. Urine protein electrophoresis showed glomerular proteinuria.

Kidney biopsy demonstrated many glomeruli with collapsing lesions with prominent podocyte intracytoplasmic protein resorption droplets (Fig 2) and diffuse acute tubular injury. Interstitial fibrosis and tubular atrophy were mild, with mild interstitial inflammation and no significant arterial thickening or hyaline arteriolosclerosis. Immunofluorescence revealed minimal nonspecific glomerular staining for immunoglobulin M and C3 (likely entrapment). Electron microscopy revealed extensive podocyte foot-process effacement and endothelial tubuloreticular structures, without electron-dense deposits or viral particles within podocytes or tubular cells.

During the hospitalization, the patient experienced improvement in his gastrointestinal symptoms and respiratory status. He completed hydroxychloroquine and methylprednisolone therapy. Despite clinical improvement, he continued to have poor solute clearance requiring hemodialysis. A tunneled central venous hemodialysis catheter was placed and at the time of publication, the patient remains dialysis dependent.

In situ analysis for the presence of SARS-CoV-2 RNA was performed on both patients using RNAScope (ACD) and failed to show evidence of viral RNA in the kidney. Apolipoprotein L1 (*APOL1*) genotyping performed on kidney biopsy tissue revealed both patients to have 2 risk alleles (G1/G2; Item S1).

DISCUSSION

The incidence of acute kidney injury in hospitalized patients with COVID-19 infection varies from 3% to 29% and is a negative prognostic marker.[1,2,5] Most kidney injury in COVID-19–infected patients is thought to be hemodynamic mediated and includes prerenal injury, acute tubular necrosis, and metabolic abnormalities, including hyponatremia, hypernatremia, hypokalemia, hyperkalemia, and metabolic acidosis. A high prevalence of proteinuria of 43.9% and hematuria of 26.7% in hospitalized patients has been noted with COVID-19 infection, suggesting underlying tubulointerstitial and possible glomerular injury.[2]

Initial kidney pathologic findings from postmortem examinations showed acute tubular injury, and immunostaining with SARS-CoV-2 nucleoprotein antibody was positive in kidney tubules.[3,4] Proposed mechanisms of kidney injury included direct cytopathic effects on kidney tissue,[2,4] as well as cytokine storm–mediated sepsis, hypoxia, and rhabdomyolysis.[6-9]

We present 2 cases of collapsing glomerulopathy associated with COVID-19 infection. The temporal association with SARS-CoV-2 infection and the presence of endothelial tubuloreticular inclusions, in the absence of any known autoimmune or other identified viral causes in our patients, strongly favor that COVID-19 infection has mediated collapsing glomerulopathy.

Collapsing glomerulopathy is a morphologic variant of focal segmental glomerulosclerosis and is associated with various conditions, including viral infections such as HIV, cytomegalovirus, and parvovirus B19; autoimmune diseases such as lupus; hemophagocytic syndrome; glomerular ischemia associated with thrombotic microangiopathy and sickle cell disease; and drug exposure such as interferon and pamidronate.[10] Collapsing glomerulopathy is known to have a higher prevalence in people of African descent and is associated with high-risk *APOL1* variants. Treatment of secondary collapsing glomerulopathy involves treatment of underlying conditions. Immunosuppressive treatment is considered if there is a rapid decline in kidney function despite treating the primary disease.

Interestingly, there are 4 additional cases of COVID-19–associated collapsing glomerulopathy that appeared in press during the past few weeks,[11-14] suggesting that collapsing glomerulopathy is an emerging and novel manifestation of COVID-19 infection. There are several similarities in clinicopathologic characteristics of these reported cases (Table S3) that merit further attention. All cases involved patients with African descent. *APOL1* genetic testing done in our patients and 2 other patients showed high-risk alleles in all.[11,13] Therefore, COVID-19–associated collapsing glomerulopathy could be due to an immune dysregulation–mediated "second hit" to podocytes in people of African ancestry with *APOL1* risk alleles. Patients had relatively mild respiratory symptoms with no documented septic shock or acute respiratory distress syndrome, suggesting that hemodynamic and severe cytokine storm–mediated kidney injury are less likely. SARS-CoV-2 in situ hybridization done in our 2 cases and 2 other cases was negative for viral RNA and no viral particles were detected in kidney tissue by electron microscopy in these patients, arguing against direct viral cytopathic effect.[11,13,14] Although these patients had recovery of their respiratory symptoms, there was persistence of significant kidney injury in all cases, with 5 of 6 requiring hemodialysis at discharge. Thus, the prognosis of COVID-19–associated collapsing glomerulopathy appears to be poor, although further larger

studies with follow-up are needed to determine the prognosis and treatment, including response to antiviral agents and immunomodulation therapy such as corticosteroids.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Additional studies

Table S1: Laboratory results on presentation

Table S2: Urinalysis on presentation

Table S3: Comparison of currently published case reports of collapsing glomerulopathy in patients with COVID 19.

ARTICLE INFORMATION

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REFERENCES

1. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
2. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97(5):829-838.
3. Diao B, Wang C, Wang R, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *MedRxiv*. Preprint 3 April 2020. https://doi.org/10.1101/2020.03.04.20031120.
4. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98(1):219-227.
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
7. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm and immunosuppression. *Lancet*. 2020;395:1033-1034.
8. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846-848.
9. Durvasula R, Wellington T, McNamara E, Watnick S. COVID-19 and kidney failure in the acute care setting: our experience from Seattle. *Am J Kidney Dis*. 2020;76(1):4-6.
10. Albaqumi M, Soos TJ, Barisoni L, Nelson PJ. Collapsing glomerulopathy. *J Am Soc Nephrol*. 2006;17(10):2854-2863.
11. Larsen C, Bourne T, Wilson J, Saqqa O, Sharshir M. Collapsing glomerulopathy in a patient with coronavirus disease 2019 (COVID-19). *Kidney Int Rep*. 2020;5(6):935-939.
12. Kissling S, Rotman S, Gerber C, et al. Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int*. 2020;98(1):228-231.
13. Peleg Y, Kudose S, D'Agati V, et al. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. *Kidney Int Rep*. 2020;5(6):940-945.
14. Gaillard F, Ismael S, Sannier A, et al. Tubuloreticular inclusions in COVID-19-related collapsing glomerulopathy. *Kidney Int*. *Kidney Int*. 2020;98(1):241.