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Collapsing Glomerulopathy in a Patient With Coronavirus Disease 2019 (COVID-19)

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the official name given by the World Health Organization to the disease caused by the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease has rapidly spread around the world after its initial recognition in Wuhan, Hubei Province, China.[1] Pulmonary involvement with diffuse alveolar damage and respiratory failure has been the major disease focus in patients with COVID-19; however, recent reports have highlighted the fact that kidney injury is also relatively common in this infection and is associated with increased morbidity and mortality.[2,3] In a large case series from China, 15.5% of patients show evidence of kidney injury on presentation with 3.2% developing acute kidney injury during hospitalization.[3] Hematuria and proteinuria are also common, being present in 27% and 44% of patients, respectively.[3] We present the clinical and renal biopsy findings in an African American patient with COVID-19. This case raises the question of whether people of African descent with high-risk *APOL1* genotype (presence of 2 risk alleles) could be at increased risk of kidney disease in the setting of COVID-19.

CASE PRESENTATION

A 44-year-old African American woman presented to the emergency department complaining of fever, vomiting, worsening cough, and flank pain. She was found to have acute kidney injury with a serum creatinine of 4.0 mg/dl superimposed on known chronic kidney disease. Urinalysis on presentation was positive for blood and protein with a spot urine protein/creatinine ratio of 3.9 g/g. Her baseline serum creatinine, measured 6 months before presentation, was 1.4 mg/dl. Baseline urinalysis before presentation showed 2+ protein with no spot urine protein/creatinine ratio collection result available. Her medical history included poorly controlled diabetes mellitus type 2, essential hypertension, dyslipidemia, and chronic kidney disease attributed to diabetes. Her past surgical history included cesarean delivery and cholecystectomy. She has never smoked. She denied drinking alcohol or illicit drugs.

Physical examination showed the patient's temperature was 102 °F (38.9 °C), blood pressure of 140/90 mm Hg, heart rate of 107 beats per minute, and a respiratory rate of 18 breaths per minute. She was breathing ambient air. She appeared ill but alert and conversational. She had no sinus tenderness, but notable pharyngeal erythema, without cervical lymphadenopathy. Both lungs were clear to auscultation. Her heart sounds were normal, and there was no murmur. Her abdomen was soft, with mild costovertebral angle tenderness and active bowel sounds. There was no erythema, tenderness, or effusion in the joints, and no skin rash was seen. Capillary fill time was 2 seconds to all digits. Extremities showed no pitting edema. She had stable and congruent mood and affect.

Laboratory results from the time of admission are detailed in Tables 1 and 2. The patient was anemic and had electrolyte abnormalities. In addition, serologic testing for hepatitis B, hepatitis C, and HIV were negative. Serum complement testing for C3 and C4 were normal. A chest X-ray showed right subsegmental atelectasis and small right-sided pleural effusion. Renal ultrasound showed normal-sized kidneys with no evidence of obstructive uropathy. The differential diagnosis at the time of admission was sepsis, acute pyelonephritis, and COVID-19. She was started on i.v. fluid support as well as ceftriaxone and vancomycin. Full acute kidney injury workup was ordered. The

Table 1. Laboratory results on presentation

Laboratory test	Reference range	Patient result
Sodium, mmol/l	135–146	133 (L)
Potassium, mmol/l	3.6–5.2	4.2
Chloride, mmol/l	96–110	101
CO_2, mmol/l	24–32	17 (L)
Glucose, mg/dl	65–99	336 (H)
BUN, mg/dl	7.0–25.0	34.0 (H)
Creatinine, mg/dl	0.50–1.10	3.85 (H)
Calcium, mg/dl	8.4–10.3	8.2 (L)
Albumin, g/dl	3.4–5.4	2.5 (L)
eGFR, ml/min	>89	16 (L)
Magnesium, mg/dl	1.5–2.6	1.9
AST, U/l	<45	29
Bilirubin, direct, mg/dl	0.0–0.3	0.1
Bilirubin, indirect, mg/dl	<1.3	0.4
Bilirubin, total, mg/dl	<1.3	0.5
Hemoglobin, g/dl	12–16	8.1 (L)
WBC count	4–11 × 10^9/μl	7.9
Platelet count	150–450 × 10^3/μl	241
Hemoglobin A1c, %	4.0–5.6	11.6 (H)

AST, aspartate aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; H, high; L, low; WBC, white blood cell.

Table 2. Urinalysis on presentation

Laboratory test	Reference range	Patient value
Amorphous crystals	None seen, rare, occasional/HPF	Rare
Appearance	Clear	Hazy (A)
Bacteria	None seen, rare/HPF	Rare
Bilirubin	Negative	Negative
Blood	Negative	>1.0 mg/dl (A)
Color	Colorless, straw, yellow, pale yellow	Yellow
Glucose	Negative, normal	≥500 mg/dl (A)
Ketones	Negative	20 mg/dl (A)
Leukocyte esterase	Negative	75/μl (A)
Mucus	None seen/LPF	Rare (A)
Nitrate	Negative	Negative
pH	4.5–8.0	6.0
Ur protein	Negative	≥500 mg/dl (A)
RBC	0–2/HPF	≥100 (A)
Renal epithelial cells	None seen/HPF	<1 (A)
Specific gravity	1.005–1.030	1.011
Squamous epithelial cells	0–20/LPF	20–100 (A)
Urobilogen	<2	0
WBC	0–5/HPF	0–5
Yeast, budding	None seen/HPF	Present (A)

A, abnormal; HPF, high-power field; LPF, low-power field; RBC, red blood cell; WBC, white blood cell.

patient was admitted to the medical floor for further evaluation and management.

Hospital Course

Over the course of 5 days, the patient developed confusion and worsening respiratory distress, requiring supplemental oxygen. She was able to maintain saturation with 2 to 3 l/min of nasal cannula. Repeat chest X-ray showed new-onset bilateral diffuse patchy opacities. Antibiotic therapy was changed from ceftriaxone to cefepime.

The patient's renal function declined over the same period, and she was placed on dialysis on hospital day 8 with a serum creatinine of 11.4 mg/dl despite good urine output (>1 l/d). A spot urine protein/creatinine ratio at the time of dialysis initiation was 25 g/g. An autoimmune workup was positive for Sjögren-syndrome–related antigen A and antinuclear antibodies. Evaluation by rheumatology showed no clinical signs of Sjögren syndrome. Serum antineutrophil cytoplasmic antibodies was negative and tests for serum complements C3 and C4 were normal. All urine and blood cultures were negative and the COVID-19 polymerase chain reaction assay was pending. A renal biopsy was performed to evaluate the etiology of the patient's renal disease.

Kidney Biopsy Diagnosis

A total of 24 glomeruli were identified in the tissue submitted for evaluation, 14 of which were globally sclerotic. Many of the intact glomeruli showed tuft collapse with overlying epithelial hypertrophy and hyperplasia in the Bowman space (Figure 1). No endocapillary hypercellularity or necrotizing lesions were present in the glomeruli. Intact portions of glomeruli showed minimal mesangial expansion. The tubular epithelium was notable for injury that was most prominent in the proximal tubules and included reactive nuclei with mitotic figures, as well as diffuse simplification with denudation of brush borders. The interstitium showed edema with an associated inflammatory infiltrate that predominantly consisted of lymphocytes and plasma cells with scattered eosinophils. No tubulitis was present. The degree of interstitial fibrosis and tubular atrophy present in the background was judged to be moderate. Direct immunofluorescence evaluation was negative for immune reactants in glomeruli, including IgA, IgG, IgM, C3, C1q, kappa, and lambda. Ultrastructural examination showed basement membranes that were slightly thickened. No immune-type electron-dense deposits were identified. There was severe foot process effacement, involving more than 90% of the glomerular basement membrane surface area. Occasional tubuloreticular inclusions were present in the glomerular endothelial cell cytoplasm. No definitive viral particles were identified by electron microscopy. A diagnosis of collapsing glomerulopathy was rendered. APOL1 genotyping on the biopsy material was performed as previously described,[4] and the patient was found to be homozygous for the G1 risk allele (rs73885319). *In situ* analysis for the presence of SARS-CoV-2 RNA was performed using RNAscope (ACD, Newark, CA) as previously described,[5] and failed to show evidence of viral RNA in the kidney (Figure 2).

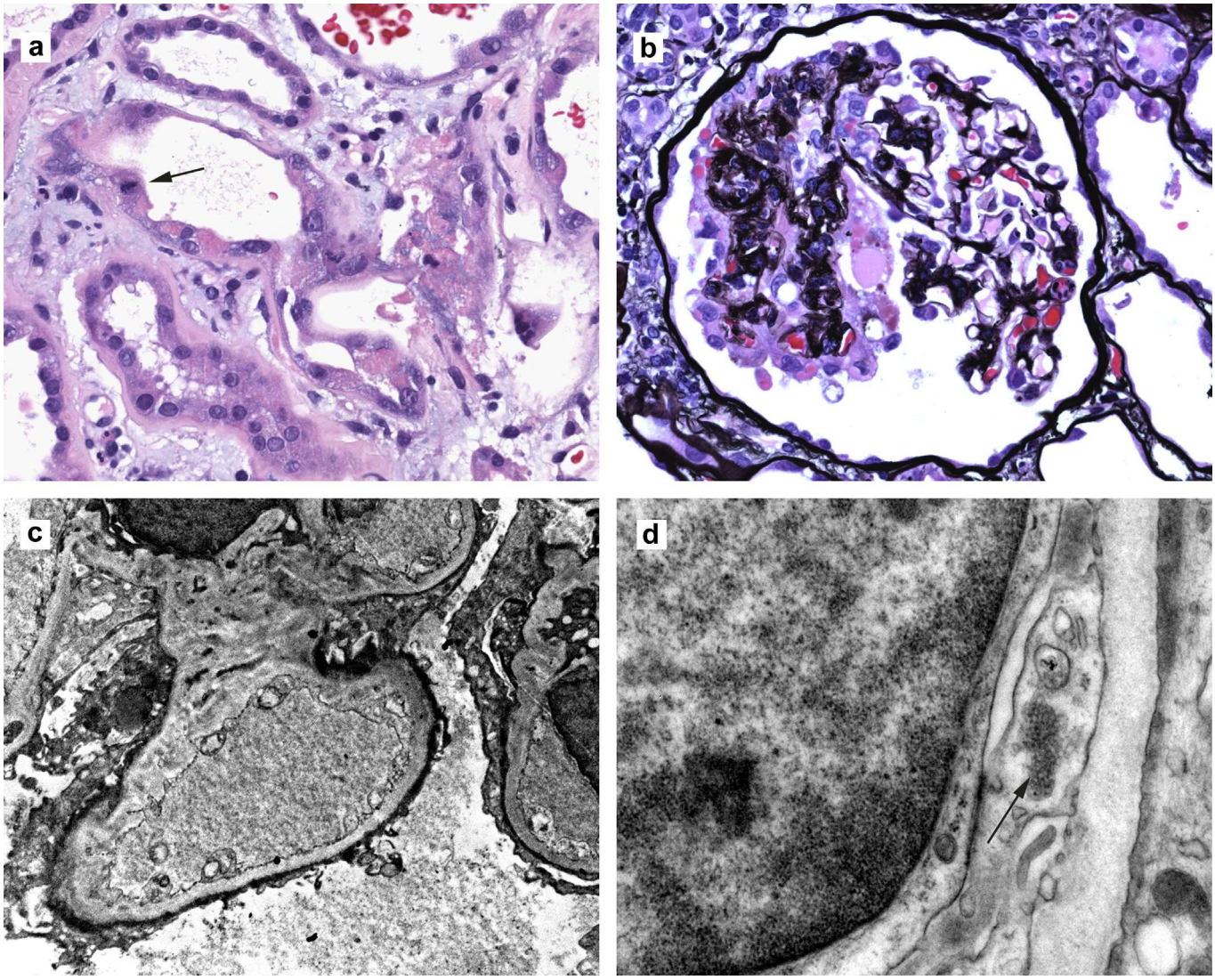

Figure 1. Renal biopsy findings. (a) Tubular epithelium with reactive nuclei including focal mitotic figures (arrow) as well as cytoplasmic simplification and denudation of brush borders (hematoxylin-eosin; original magnification ×400). (b) Glomerulus with tuft collapse and overlying epithelial hypertrophy and hyperplasia (Jones methenamine silver; original magnification ×400). (c) Ultrastructural examination reveals extensive foot process effacement (original magnification ×6000). (d) Tubuloreticular inclusions (arrow) within a glomerular endothelial cell (original magnification ×30,000).

Follow-up

Shortly after the biopsy was ordered, the COVID-19 polymerase chain reaction assay returned as positive. The patient's clinical status markedly improved with dialysis. Her confusion resolved and she no longer required oxygen support. She continued to have good urine output, albeit without proper clearance, mandating further hemodialysis on an outpatient basis. A Permacath was placed and dialysis chair placement was arranged as such. Repeat COVID testing 5 days after initial test was still positive.

DISCUSSION

Possible mechanisms for kidney injury in COVID-19 include direct infection of the kidney as well as cytokine storm related to sepsis. Direct infection of the renal parenchyma is possible because the renal proximal tubule cells highly express angiotensin-converting enzyme 2, the cellular entry receptor for the SARS-CoV-2 virus.[6,7] The virus likely gains access to the kidney through the bloodstream, as approximately 15% of patients were found to have RNAemia in one series.[2] Cytokine storm has been described previously both in animal models and humans infected with other highly pathogenic human coronaviruses, including severe acute respiratory syndrome and Middle East respiratory syndrome.[8,9,S1] Evidence of cytokine storm has also been documented in patients with COVID-19.[2,S2]

This case report is the first renal biopsy report to our knowledge describing the renal biopsy findings

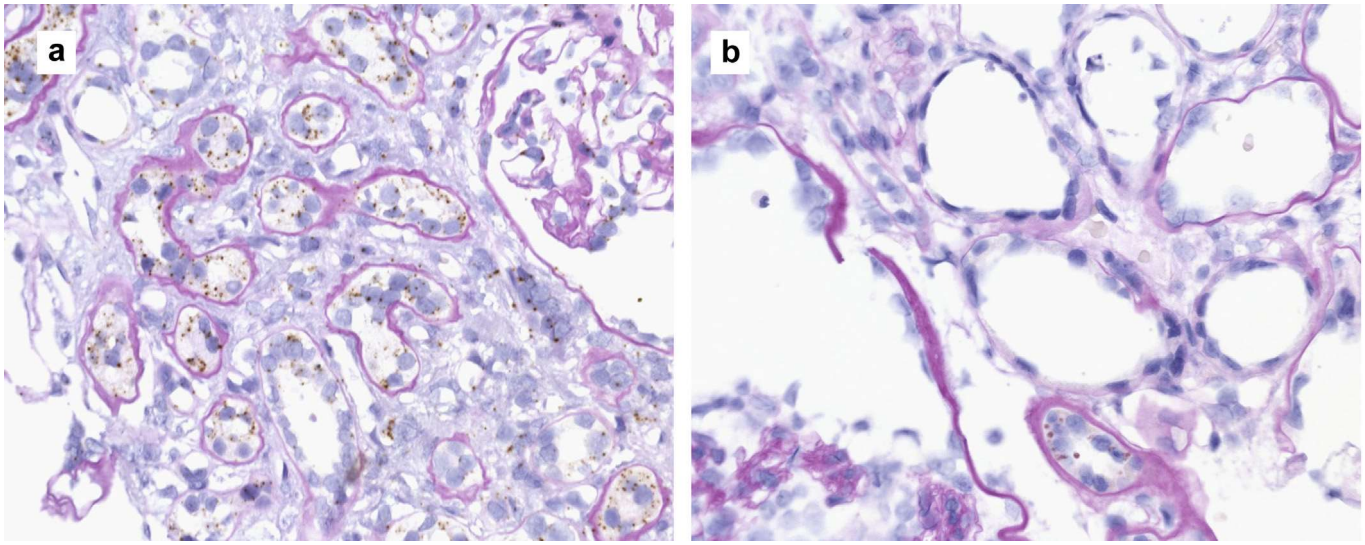

Figure 2. *In situ* hybridization for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (a) Tissue quality was evaluated by performing RNAscope analysis for mRNA of the housekeeping gene peptidylprolyl isomerase B (*PPIB*). Positive cytoplasmic staining confirms adequate quality. Signal was detected using 3,3′-diaminobenzidine (DAB) (brown) chromogen. (periodic acid–Schiff counter stain; original magnification ×400). (b) RNAscope using probes directed against SARS-CoV-2 shows absence of signal in the patient's kidney parenchyma (periodic acid–Schiff counter stain; original magnification ×400).

in a living patient with COVID-19. A recent report of postmortem kidney tissue from 6 patients who died of COVID-19 showed acute tubular injury without glomerular abnormalities.[S3] The SARS-CoV-2 NP antigen was described in renal tubules by immunohistochemical analysis in this report when the renal tissue was reacted with a rabbit monoclonal antibody directed against the SARS-CoV-2 nucleoprotein (Clone ID: 019; Sino Biological, Beijing, China). In our laboratory, immunohistochemical analysis of renal tissue using this antibody under numerous conditions showed nonspecific positive staining in the renal parenchyma of all kidneys. In the case presented here, *in situ* hybridization analysis for SARS-CoV-2 failed to show evidence of viral RNA in the kidney, suggesting that direct infection of the kidney was not present. However, we cannot exclude the possibility that the virus was present below the level of detection. The biopsy from our patient is unique, as it demonstrates the presence of collapsing glomerulopathy. Acute tubular injury is commonly present on biopsy in association with collapsing glomerulopathy, and, therefore, is not necessarily being driven by either direct viral infection of the kidney or cytokine storm. The biopsy findings raise the question as to whether or not African American patients who contract COVID-19 are at increased risk of developing *APOL1*-related kidney disease.

The reports of kidney disease in patients with COVID-19 thus far are primarily limited to Chinese patients, and therefore might not be generalizable to other populations, such as the African American patient described here. In fact, African American individuals have long been known to be at increased risk of developing kidney disease compared with other ethnicities without recent African ancestry.[S4] This increased risk has been shown to largely result from 2 risk alleles in the *APOL1* gene, G1 and G2, that are very common.[S5] Approximately 39% of African American individuals possess one *APOL1* risk allele and 13% are at increased risk of kidney disease as a result of homozygosity for *APOL1* risk alleles.

Collapsing glomerulopathy is the most fulminant form of kidney disease in the *APOL1* spectrum. It is an aggressive form of glomerular injury that has been described in association with autoimmune disease, interferon therapy, and viral illnesses including HIV, cytomegalovirus, and parvovirus.[S6–S10] Regardless of the associated disease, approximately 70% of these patients with collapsing glomerulopathy are homozygous for *APOL1* risk alleles. The etiology of *APOL1*-associated nephropathy has not been definitively determined, although there are data to support the role of innate immune pathways upregulated in viral illnesses and autoimmune disease as key drivers.[S10] The renal biopsy findings in the case presented here are therefore concerning for an aggressive *APOL1*-associated collapsing glomerulopathy driven by a COVID-19–related cytokine storm. However, it is also possible that the collapsing glomerulopathy is unrelated to the viral infection and was only brought to medical attention by the SARS-CoV-2 infection.

Table 3. Key teaching points

1.	*In situ* hybridization analysis for SARS-CoV-2 failed to show evidence of viral RNA in the kidney, suggesting that direct infection of the kidney was not present.
2.	Immunohistochemical analysis using a SARS-CoV-2 nucleoprotein antibody previously shown to have positive staining in the kidney of patients with COVID-19 showed nonspecific positive staining in the renal parenchyma of all kidneys in our laboratory.
3.	This case raises the question of whether people of African descent with high-risk *APOL1* genotype (presence of 2 risk alleles) could be at increased risk of kidney disease in the setting of COVID-19.

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

We present a case of collapsing glomerulopathy in an African American patient with COVID-19 who had rapid decline in renal function. This case raises the possibility that African American individuals with high-risk *APOL1* genotype could be at increased risk of kidney disease in the setting of COVID-19. Additional investigation to determine if *APOL1* risk alleles confer increased risk of morbidity and mortality deserves urgent study, as it could have important implications for this population (Table 3).

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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