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Single Case

Tip Lesion Variant of Focal and Segmental Glomerulosclerosis in a COVID-19 Patient

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Acute kidney injury · Proteinuria · Renal biopsy · SARS-CoV-2

Abstract
Acute kidney injury is a common complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Several pathologic findings are continually being reported, showing a probably multifactorial etiology. The authors present a case of a patient diagnosed with a tip lesion variant of focal segmental glomerulosclerosis (FSGS) in the setting of COVID-19. A 43-year-old African American female with no known renal disease presented to the emergency department with a 6-day history of fatigue, headache, hypoageusia, myalgia, cough, nausea, and vomiting. Laboratory tests confirmed SARS-CoV-2 infection. During hospitalization, there was a progressive decline in kidney function and evidence of nephrotic-range proteinuria without nephrotic syndrome. Biopsy specimen showed a tip lesion variant of FSGS. Genetic test revealed a homozygous variant of uncertain clinical significance (c.397G>A [p.V133M]) in the *epithelial membrane protein 2* (*EMP2*) gene. To our knowledge, this is the first case report of a tip lesion in a COVID-19 patient with no renal history. More studies are warranted to define susceptible groups and identify the detailed mechanisms of COVID-19-related kidney disease that would allow for specific management of this complication.

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Introduction

Coronavirus disease 2019 (COVID-19), a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan in December 2019 and quickly become a major health public problem worldwide [1, 2]. Although COVID-19 is primarily considered a respiratory illness, it is also associated with deleterious effects on many other organ systems, including the kidneys [3]. Renal manifestations may include the presence of proteinuria, hematuria, and acute kidney injury (AKI). Studies report an incidence of AKI ranging from 1% to 42% in hospitalized patients, with a higher incidence in critically ill patients. Additionally, the presence of renal impairment has been strongly associated with greater in-hospital morbidity and mortality [4–8]. Case reports, small series, and autopsy studies have reported a wide spectrum of glomerular and tubular diseases in COVID-19 patients [9–16]. New data on the exact pathophysiologic mechanisms of COVID-19-related kidney disease are continually being published showing a probably multifactorial etiology [17]. Here, we report the first case of a COVID-19 patient with no known renal disease diagnosed with a tip lesion variant of focal and segmental glomerulosclerosis (FSGS).

Case Report

A 43-year-old African American female with a medical history of pulmonar tuberculosis treated 14 years ago presented to the emergency department with a 6-day history of fatigue, headache, hypoageusia, myalgia, cough, nausea, and vomiting. Along with that, the patient complained of shortness of breath and right-sided pleuritic chest pain in the last 24 h. She underwent a nasopharyngeal swab for SARS-CoV-2 reverse-transcriptase-polymerase chain reaction (RT-PCR) test that resulted positive and she was hospitalized at the COVID-19 unit. Upon admission, the vitals were as follows: blood pressure 107/73 mm Hg, pulse rate 64 beats/min, temperature 35.5°C, respiratory rate 16 breaths/min, and oxygen saturation 98% on room air. Her physical examination was unremarkable, except for the mild epigastric tenderness without muscle guarding or rebounding pain. Blood tests showed mild lymphopenia 1,200 × 10^9/L, thrombocytopenia 114 × 10^9/L, albumin 3.6 mg/dL, and C-reactive protein 6 mg/L, with normal renal function and serum liver tests. Urinalysis revealed protein 4+ and erythrocytes 3+, obtained during the menstrual period.

Intravenous fluid therapy and antiemetics were initiated with symptom improvement of nausea and vomiting. Despite hydration, there was a progressive decline in kidney function with a peak serum creatinine level of 1.6 mg/dL on day 7 of hospitalization, with blood urea nitrogen of 20 mg/dL and preserved diuresis. She developed dark colored urine and repeated urinalysis, at time when there was no menstrual bleeding, showed 3 red blood cells/high-power field, 5 white blood cells/high-power field, and urinary protein excretion of more than 500 mg/dL. A 24-h urine protein quantification revealed 13.4 g. Laboratory results are detailed in Table 1.

Renal ultrasonography showed significant loss of corticomedullary differentiation. Both renal size and parenchymal thickness were preserved bilaterally and there was no evidence of hydronephrosis.

Serologic workup was positive for antinuclear antibodies with a nucleolar pattern and negative for anti-doublestranded DNA, anti-neutrophilic cytoplasmic antibodies, circulating cryoglobulins, human immunodeficiency virus, and hepatitis C. Results were also positive for past hepatitis B virus infection: a positive hepatitis B core antibody with a negative hepatitis B surface antibody and hepatitis B surface antigen. Serum protein electrophoresis showed an inflammatory pattern with polyclonal hypergammaglobulinemia and serum immunofixation did not reveal any monoclonal immunoglobulin. There was no complement consumption.

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Table 1. Laboratory data on admission and on day 7

Parameters	Reference range	On admission	Day 7
Hemoglobin, g/dL	12–15	13.7	12
Absolute WBC count, $\times 10^9$/L	4–10	4.6	4.5
Absolute neutrophil count, $\times 10^9$/L	2–7	2.9	3.1
Absolute lymphocyte count, $\times 10^9$/L	1.5–4	1.2	1.0
Absolute platelet count, $\times 10^9$/L	150–400	114	133
BUN, mg/dL	7–18.7	20	20
Creatinine, mg/dL	0.6–1.1	1.0	1.6
Sodium, mmol/L	136–144	143	142
Potassium, mmol/L	3.3–5.1	3.5	3.8
Albumin, g/dL	3–5	3.6	1.46
C-reactive protein, mg/L	<5	6	23
Procalcitonin, ng/mL	<0.5	<0.05	–
Urinalysis protein	Negative	4+	4+
Urinalysis blood	Negative	3+	2+
Urine RBC	0–2/hpf	<1	3
Urine WBC	0–2/hpf	2	5
24-h urine protein (g/24 h)	<0.3	–	13.4

WBC, white blood cell; BUN, blood urea nitrogen; RBC, red blood cell; hpf, high-power field.

Treatment with low-dose angiotensin-converting-enzyme (ACE) inhibitor was initiated. After discontinuation of COVID-19 isolation, a kidney biopsy was performed to determine the cause of AKI with nephrotic-range proteinuria. On light microscopy, five glomeruli were present for evaluation: one was globally sclerotic, one revealed a focal adhesion of the glomerular tuft to Bowman's capsule (Fig. 1a), one showed an expansion of the glomerular tuft to the proximal tubule (Fig. 1b), and the remaining showed no changes. The interstitium showed mild edema and there was mild interstitial fibrosis (<5%). There were foci of acute cellular necrosis, without tubular atrophy. Arterioles were well preserved. Congo-red stain was negative. Immunofluorescence showed segmental deposition of complement C3. Based on these findings, the diagnosis of tip lesion variant of FSGS was made. No corticosteroid therapy was started because her 24-h urine proteinuria decreased to 1,022 mg/24 h 1 week after introduction of ACE inhibitor with serum creatinine of 1.3 mg/dL, along with the resolution of other COVID-19 symptoms.

The patient returned home 20 days after hospitalization. After 1 month of discharge, her serum creatinine decreased to 1.1 mg/dL, while proteinuria persisted at subnephrotic levels (1,060 mg in the 24-h urine protein collection). An enlarged nephrotic syndrome panel testing of 67 genes was performed, which identified a homozygous variant of uncertain clinical significance (c.397G>A [p.V133M]) in the *epithelial membrane protein 2* (*EMP2*) gene.

Discussion

The etiology of renal involvement in COVID-19 cases is not fully understood. The spectrum of pathological findings is beginning to emerge, showing that COVID-19 affects the tubular, glomerular, and vascular compartments. The predominant finding in living patients and

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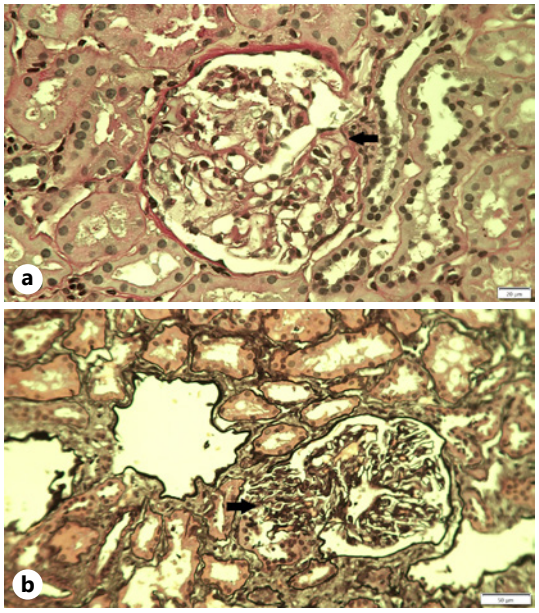

Fig. 1. Tip lesion variant of FSGS in a patient with COVID-19. **a** Focal adhesion of the glomerular tuft to Bowman's capsule. Periodic acid Schiff: magnification, ×400. **b** Expansion of the glomerular tuft to the proximal tubule. Jones methylamine silver: magnification, ×250.

autopsy series that have been published to date was acute tubular necrosis, with ischemia as the most common trigger. On its turn, collapsing glomerulopathy is likely the most common glomerular disease [18]. The exact mechanisms of renal injury due to COVID-19 are unclear, with some suggesting renal tropism of SARS-CoV-2, whereas in the rest direct viral effect was ruled out as possible etiology for renal injury [19]. In fact, it seems that viral infection may affect the immune system with triggering of glomerular diseases. Several other glomerulopathies have been reported in association with COVID-19 such as proliferative glomerulonephritis with monoclonal Ig deposits, crescentic glomerulonephritis, and minimal change disease, but whether this fact is directly related to SARS-CoV-2 infection or if this infection acts as a trigger in patients with predisposition is subject for further investigation [20].

This case demonstrates a tip lesion variant of FSGS in the setting of COVID-19. FSGS describes a renal histologic lesion with diverse etiologies and pathogenic mechanisms that are linked by podocyte injury and depletion (podocytopathy), whose cardinal clinical feature is nephrotic-range proteinuria [21]. The lesion of FSGS can be subdivided into primary ("idiopathic"), genetic, and secondary forms. Secondary FSGS usually does not develop complete nephrotic syndrome and comprises virus-associated FSGS (e.g., human immunodeficiency virus 1, Epstein-Barr virus, cytomegalovirus, and parvovirus B19), which typically improves with resolution of the infection. Several susceptibility genes may confer an increased risk of FSGS, which manifests after the imposition of genetic or environmental second hits. The best known of these are the G1 and G2 polymorphisms in the *apolipoprotein L1* (*APOL1*) gene in African Americans, which confer a much higher risk of collapsing glomerulopathy [22]. The genetic test of the patient revealed a homozygous variant of uncertain clinical significance (c.397G>A [p.V133M]) in EMP2. Gee HY et al. identified several other EMP2 mutations as causing an autosomal recessive form of nephrotic syndrome (type 10), characterized by FSGS. At the cellular level, depletion of EMP2 in podocytes and endothelial cells of glomeruli appears to result in an increased amount of CAVEOLIN-1 and decreased cell proliferation [23].

The specific pathophysiology of tip lesion has not yet been defined [24]. In this particular case, the patient had a potential genetic susceptibility due to EMP2, and COVID-19 infection was a second hit. In secondary FSGS, treatment of the underlying cause of the disease can reverse or slow down the progression of renal impairment [25]. The patient showed improvement

in renal function with reduction in proteinuria at subnephrotic levels after the introduction of ACE inhibitor and resolution of SARS-CoV-2 infection, the latter with no specific proven treatment at the time.

A PubMed search was conducted by the authors in January 2022 with the terms "tip lesion FSGS" + COVID-19 and "tip lesion FSGS" + SARS-CoV-2, which revealed only one case of tip lesion FSGS on the background of chronic allograft nephropathy in a SARS-CoV-2-infected renal transplant patient [26]. It seems to be a rare presentation in COVID-19, which may infer that this pathologic finding occurs only in genetically predisposed individuals. However, it is important to mention that the percentage of patients with COVID-19-associated kidney disease that undergo a kidney biopsy remains low, which is related to various specific factors of COVID-19, including the use of mechanical ventilation, anticoagulation requirements, and logistical issues given the risk of viral transmission.

It is reasonable to proceed with kidney biopsy in COVID-19 patients who have AKI and additional clinical features that suggest glomerular injury for both diagnostic and prognostic reasons. Urine analysis and protein to creatinine ratio obtained at the admission of patients with SARS-CoV-2 infection may enable earlier recognition of associated glomerulopathies.

The authors present a rare kidney pathologic finding in the setting of COVID-19 in a patient with a potentially high-risk EMP2 variant for the development of glomerular disease. More studies are warranted to define susceptible groups and identify the detailed mechanisms of COVID-19-related kidney disease that would allow for specific management of this complication. This case report also highlights the importance of kidney biopsy to determine the etiology of renal involvement. The CARE Checklist has been completed by the authors for this case report, attached as supplementary Material (for all online suppl. material, see www.karger.com/doi/10.1159/000528029).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joint first authorship for Rita Afonso and Roberto Calças Marques. Henrique Borges, Eduarda Carias, and Ana Teresa Domingos provided clinical assistance and made a substantial contribution to the concept and design of the manuscript. Ana Cabrita provided clinical assistance, as well as revised the manuscript critically, and contributed important intellectual content. Sandra Sampaio provided clinical assistance. Ana Paula Silva revised the manuscript critically

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Data Availability Statement

All data that support the findings of this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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