Case Report

COVAN Leading to ESKD Despite Minimal COVID Symptoms

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Abstract
We report a case of dialysis dependence in a patient with COVID-19-associated nephropathy (COVAN) who had minimal respiratory manifestations. A 25-year-old man with a history of multiple sclerosis in remission presented with mild dyspnea due to COVID-19 pneumonia and was found to have rapidly worsening kidney function. He only required nasal cannula and was able to be weaned off within a few days. Despite having only mild respiratory disease, his kidney function worsened and urgent hemodialysis was started for hyperkalemia and uremic encephalopathy. Kidney biopsy demonstrated collapsing glomerulopathy due to COVID-19 with moderate interstitial fibrosis and tubular atrophy. His kidney function did not recover, and he unfortunately now has been dependent on hemodialysis for over 3 months. Multiple case reports have described COVAN causing dialysis dependence, but to our knowledge this is the first reported case of COVAN causing dialysis dependence in a patient with such mild respiratory disease. Currently the indications for intensive COVID-19 therapies are based on oxygen requirements. This case demonstrates that the oxygen requirement may not fully reflect the severity of COVID-19 and raises the question of whether these therapies should be considered in patients with COVAN.

Keywords
nephrology, covan

Introduction
Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV2), is known to cause acute kidney injury (AKI) in hospitalized patients. The prevalence of AKI due to COVID-19 has been reported in up to 46% of patients1 and is associated with poor prognosis, progression to chronic kidney disease (CKD), and the need for kidney replacement therapy.2-4 The most common etiology of AKI is acute tubular injury.5-8 However, collapsing glomerulopathy (also known as COVID-19-associated nephropathy or COVAN) has become increasingly more reported, especially in individuals of African descent with apolipoprotein L1 (APOL1) risk alleles.9,10 Here, we present the case of a 25-year-old Nigerian-American man whose only medical history is multiple sclerosis in remission on biannual rituximab for 10 years. Two weeks prior to presentation, he had presented to another hospital for the same symptoms and tested positive for COVID-19. The patient required only nasal cannula. He was noted to have acute kidney injury with creatinine 2.57 mg/dL (baseline 0.9-1 as of 3 years ago). He declined serologic workup or biopsy at that time. Creatinine remained stable throughout admission, and after a week-long course of intravenous dexamethasone 6 mg daily, he was discharged with a creatinine of 2.37 mg/dL. His dyspnea however never fully resolved, so he re-presented to our hospital within 5 days.

His only complaint at this point was mild dyspnea. He denied frank hematuria, dysuria, decreased urination, foamy

Case Report
A 25-year-old Nigerian-American man presented to the emergency room with shortness of breath. He was not vaccinated against COVID-19 and had a history of well-controlled multiple sclerosis on biannual rituximab for 10 years. Two weeks prior to presentation, he had presented to another hospital for the same symptoms and tested positive for COVID-19. The patient required only nasal cannula. He was noted to have acute kidney injury with creatinine 2.57 mg/dL (baseline 0.9-1 as of 3 years ago). He declined serologic workup or biopsy at that time. Creatinine remained stable throughout admission, and after a week-long course of intravenous dexamethasone 6 mg daily, he was discharged with a creatinine of 2.37 mg/dL. His dyspnea however never fully resolved, so he re-presented to our hospital within 5 days.

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urine, swelling, rashes, or joint pains. His family history was notable for lupus nephritis in his sister, which was now in “remission,” and never necessitated dialysis. Unfortunately, he was unable to provide additional information about her lupus nephritis history, including the class of nephritis or prior APOL1 testing. Family history was otherwise negative. He denied illicit drug use, tobacco use, or heavy alcohol use.

In the emergency department, vitals showed an oxygen saturation of 93% to 95% on room air, temperature of 101.4 Fahrenheit, heart rate 93–110 bpm (beats per minute), and blood pressure 91/58 mmHg. On examination, he was in no acute distress. His lungs had diffuse rhonchi, and he had no peripheral edema or rashes. Chest X-ray revealed diffuse infiltrates consistent with COVID-19 infection and was unchanged from imaging performed at the outside hospital.

His laboratory data demonstrated his creatinine had now worsened to 5.77 mg/dL from 2.37 six days prior (Figure 1). The rest of his laboratory data on admission is demonstrated in Table 1: sodium 129 mmol/L, potassium 5.7 mmol/L, bicarbonate 17 mmol/L, blood urea nitrogen 88 mg/dL, white blood cell count 14.72 /µL, hemoglobin 15.2 g/L, platelets 249,000 /µL, albumin 1.9 mg/dL, venous blood gas pH 7.31, pCO2 40, and lactate 1.4. Urine microscopy demonstrated protein, fatty casts, 1 granular cast, and rare monomorphic red blood cells. Urine protein-creatinine ratio was 12.6 g/g (1.4 g/mmol). On review of his prior studies, 100–300 protein had been noted on dipstick urinalysis 3 years ago, although urine protein-creatinine ratio had never been quantified. The following serologic workup was all normal or negative: anti-nuclear antibody, anti-double stranded DNA, C3/C4, anti-nuclear cytoplasmic antibodies, anti-phospholipase antibody, hepatitis B/C, HIV, creatinine kinase, serum protein electrophoresis, serum immunofixation, and free light chain ratio.

Creatinine drastically rose from 5.77 mg/dL on admission to 11 mg/dL within only 4 days (Figure 1). Blood urea nitrogen rose at the same time from 88 mg/dL to 162 mg/dL, and potassium was persistently 5.7 to 6 mg/dL despite

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**Figure 1.** Trend of blood urea nitrogen and creatinine after presentation to outside hospital (OSH).

**Table 1.** Pertinent Admission Labs.

| Admission labs                        |  |
|--------------------------------------|---|
| Sodium (mmol/L)                      | 129 |
| Potassium (mmol/L)                   | 5.7 |
| Bicarbonate (mmol/L)                 | 17  |
| Blood urea nitrogen (mg/dL)          | 88  |
| Creatinine (mg/dL)                   | 5.77 |
| Albumin (mg/dL)                      | 1.9 |
| Urine protein-creatinine ratio (g/mmol) | 12 |
| White blood cell count (cells/µL)    | 14,720 |
| Hemoglobin (g/L)                     | 15.2 |
| Platelets (cells/µL)                 | 249,000 |

Conversion factor for units: serum creatinine in mg/dL to µmol/L, x88.4; blood urea nitrogen in mg/dL to mmol/L, x0.357.
administering potassium chelators, loop diuretics, and insulin. He became encephalopathic with confusion and disorientation, so emergent dialysis was started for uremic encephalopathy and refractory hyperkalemia.

Although his kidney failure worsened, his COVID-19 symptoms remained minimal. His maximum oxygen requirement was nasal cannula 6 liters which was weaned off after an additional 5-day course of intravenous dexamethasone 6 mg daily. As per infectious disease consult, he was considered not to be indicated for other COVID-19 treatments including remdesivir, monoclonal antibody infusion, or baricitinib. He did not receive hydroxychloroquine, since by that time it was no longer recommended for COVID-19.

Kidney biopsy was performed shortly before dialysis was started, which was 4 days after presentation, and demonstrated collapsing focal segmental glomerulosclerosis consistent with a diagnosis of COVAN (Figures 2-4). Moderate interstitial fibrosis and tubular atrophy were seen (Figure 5) with global collapse of capillary tufts (Figure 6). Immunofluorescence showed nonspecific chunky staining of glomerular protein reabsorption droplets for C3 (3+) and C1q (1+) and was otherwise negative. Multiple attempts were made to wean him off dialysis with no success. Ultimately, he was discharged on thrice-weekly dialysis with no signs of recovery in the subsequent 3 months.

Discussion
Cases of long-term dialysis dependence due to COVAN have only been reported in patients who required intubation or positive-pressure ventilation.1,11-15 To our knowledge, this is the first reported case of COVAN causing dialysis dependence in a patient with such mild respiratory disease that he only required nasal cannula. While there are cases of patients

![Figure 2](image2.png)
**Figure 2.** High-powered Periodic acid-Schiff (PAS) light microscopy demonstrated glomeruli with features consistent with collapsing glomerulopathy. One such glomerulus is depicted above.

![Figure 3](image3.png)
**Figure 3.** High-powered PAS light microscopy demonstrated glomeruli with features consistent with collapsing glomerulopathy. Another such glomerulus is depicted above.

![Figure 4](image4.png)
**Figure 4.** Electron microscopy demonstrated that podocytes are slightly enlarged with moderate foot process effacement (70% of glomerular basement membrane surface area). No electron dense deposits observed. Tubules show loss of borders and protein reabsorption droplets.

![Figure 5](image5.png)
**Figure 5.** Low-powered Hematoxylin-and-Eosin (H&E) light microscopy demonstrated moderate interstitial fibrosis and tubular atrophy compromising approximately 30% of the parenchyma.
with lower oxygen requirements requiring dialysis, these were only in the acute setting, and the patients were discharged off of dialysis.\textsuperscript{13,16} We described a case of a young active 25-year-old with multiple sclerosis in remission, who is now unfortunately dialysis-dependent due to collapsing glomerulopathy from COVAN.

Multiple reports have suggested that the APOL1 genotype raises the risk for more severe COVAN disease.\textsuperscript{13,16,17} Considering our patient’s African background, prior protein in his dipstick urinalysis, and positive family history for lupus nephritis in his sister, we have a strong suspicion that he has the high-risk APOL1 genotype. He however declined genetic testing.

COVAN was first described in 2020 in a woman with COVID-19 who underwent kidney biopsy which revealed collapsing glomerulopathy with endothelial tubuloreticular lesions.\textsuperscript{11} The biopsy findings are very similar to those found in HIV-associated nephropathy.\textsuperscript{10} One possible mechanism for the collapsing glomerulopathy seen in COVID-19 is high levels of inflammation causing damage to podocytes.\textsuperscript{10} To support this theory, Meliambro et al recently published that immunostaining of COVAN kidney biopsies revealed increased expression of phospho-STAT3 (signal transducer and activator of transcription 3), which is activated by the inflammatory marker interleukin-6.\textsuperscript{9}

Another putative mechanism for this nephropathy is viral particle deposition in podocytes.\textsuperscript{15} This mechanism remains controversial since not all biopsies of collapsing glomerulopathy in COVID-19 have revealed viral particles.\textsuperscript{10} It also remains unclear if these particles are truly viruses since they are similar in morphology to intracellular components such as clathrin-coated vesicles and multivesicular bodies.\textsuperscript{10,15,18}

Not only is the medical community unsure of the pathophysiology of COVAN, but we are also unsure of how to treat it. No treatments have been tried in the literature other than therapies for respiratory COVID-19. Currently the indications for intensive therapies for COVID-19 such as tocilizumab and convalescent plasma are primarily based on oxygen requirements.\textsuperscript{19} However, this case demonstrates that the severity of COVID-19 may not only be based on the oxygen requirement, since our patient is now dialysis-dependent despite a low oxygen requirement. Based on current guidelines, he was not indicated for these more intensive treatments, so he only received dexamethasone.\textsuperscript{19} This raises the question of whether initiating these therapies early would have changed the course of his kidney failure, and whether acute kidney injury should be an indication for these therapies. This case also highlights the challenges of predicting which patients will develop COVAN, particularly since his respiratory COVID-19 was so mild and yet his COVAN was so severe. The outcome of dialysis dependence in such a young man was sobering, and emphasizes the urgency to elucidate this disease process and to develop targeted treatments.

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**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

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