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# A Rare Case of Granulomatous Interstitial Nephritis in a Patient With COVID-19

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**Abstract**

Acute kidney injury (AKI) in patients with coronavirus disease 2019 (COVID-19) is common, especially among severely ill patients. While acute tubular necrosis (ATN) is one of the most common findings in published kidney biopsy series for patients with COVID-19 infections, a number of glomerular pathologies have been described as well. Among glomerular pathologies in COVID-19, COVID-19-Associated Collapsing Glomerulopathy (COVAN) remains the most common pattern of injury. Patients with 2 high-risk APOL1 alleles appear to be at increased risk for COVAN, similar to other forms of collapsing glomerulopathy such as HIV-Associated Nephropathy. Acute interstitial nephritis (AIN) is a less common finding in patients with COVID-19 and reported cases have been mild. Reports of a subtype of AIN, granulomatous interstitial nephritis (GIN), among COVID-19 patients are extremely rare and have not been reported in association with COVAN. Here, we report a case of COVAN associated with severe GIN.

**Keywords**

nephrology, AKI, COVAN, GIN, AIN, COVID-19

## Case Presentation

A 52-year-old man with a past medical history of multiple sclerosis (MS) not on immunosuppression and chronic kidney disease (baseline serum creatinine 1.6 mg/dL) presented to our hospital with fever, cough, and fatigue. His symptoms started a few weeks prior to presentation, and his symptoms persisted despite the use of nonsteroidal anti-inflammatory drugs (NSAIDs). A few days prior to the presentation, he developed decreased urination. He denied joint pain, arthralgias, abdominal pain, diarrhea, nausea, vomiting, hematuria, chest pain, rash, uveitis, and periorbital or leg edema. He was not on home medications and denied any other over-the-counter medications. He denied a history of smoking, alcohol, or recreational drug use. His first cousin had a history of end-stage kidney disease at age 50, and the patient had a strong family history of hypertension (HTN). Due to previous MS flares after vaccination, the patient did not receive the coronavirus disease 2019 (COVID-19) vaccine.

On initial presentation to our hospital, his vital signs were as follows: temperature, 101.3°F; heart rate, 88; respiration, 24; blood pressure, 116/79; SpO2, 96% on room air; and weight, 94.2 kg. The physical examination was remarkable for bilateral lung crackles. Peripheral edema was absent. The patient tested positive for SARS-CoV-2 in the emergency room and was found to have oliguric kidney failure, presenting with a creatinine of 9.6 mg/dL that uptrended to 13.7 mg/dL on hospital day 4 despite resuscitation and therefore hemodialysis was initiated. Table 1 summarizes relevant lab trends over time. Table 2 summarizes serologies and infectious workup. A kidney ultrasound revealed kidney size (12.1 cm left, 12 cm right) and an increased echogenicity in the right kidney, but without the presence of stones or hydronephrosis. A kidney duplex ultrasound was negative for thrombosis. A kidney biopsy was performed on day 14.

## Pathology

The kidney biopsy revealed up to 32 glomeruli by light microscopy, 4 of which were globally sclerotic/obsolescent and none were segmentally sclerotic. Up to 4 glomeruli displayed features of glomerular collapse, characterized by the collapse of the glomerular tuft with overlying podocyte

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**Table 1.** Summary of Laboratory Evaluations and Relevant Trends.

| | | Time and events after hospital presentation (day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | iHD initiation | Started on IV methylprednisolone (1000 mg/day) | Started on 1 mg/kg/d of PO Pred | Last iHD session | Switched to Pred 100 mg q.o.d | Started on losartan/hctz | Started Pred tapering | Last follow-up visit (on prednisone 20 mg q.o.d) |
| | | Day | | | | | | | |
| Measure | Reference | 4 | 18 | 21 | 27 | 63 | 64 | 77 | 121 |
| Sodium (mmol/L) | 137-145 | 124 | | | | | | | |
| Potassium (mmol/L) | 3.5-5.1 | 5.8 | | | | | | | |
| Chloride (mmol/L) | 98-109 | 84 | | | | | | | |
| Carbon dioxide (mmol/L) | 21-31 | 14 | | | | | | | |
| Blood urea nitrogen (mg/dL) | 2-25 | 131 | | | | | | | |
| Creatinine (mg/dL) | 0.6-1.30 | 13.7 | 7.34 | 5.95 | 2.5 | | 1.5 | 2.07 | 1.8 |
| Calcium (mg/dL) | 8.3-10.5 | 6.9 | | | | | | | |
| Albumin (g/dL) | 3.5-5.7 | 2.5 | 2.4 | 2.4 | 2.9 | | 3.4 | 3.8 | 4 |
| White blood cell count ($10^3/\mu L$) | 3.5-10.5 | 8.5 | | | | | | | |
| Absolute lymphocyte count ($10^3/\mu L$) | 1.0-4.0 | 0.9 | | | | | | | |
| Hemoglobin (g/dL) | 13.0-17.5 | 15.5 | | | | | | | |
| Platelets ($10^3/\mu L$) | 140-390 | 255 | | | | | | | |
| Urine protein: urine creatinine ratio (g/g) | | >2000/39.1 | >2000/50.1 | | 7.75 | | 5.25 | 4.39 | 4.04 |
| Urine RBC (per hpf) | 0-3 | 4-10 | | | 0-3 | | | | |
| Triglycerides (mg/dL) | <150 | 251 | | | | | | | |
| Total cholesterol (mg/dL) | <170 | 164 | | | | | | | |
| Hemoglobin A1c (%) | 4.0%-5.6% | 6.0 | | | | | | | |
| CRP (mg/L) | 0-10 | 122 | | | | | | | |
| LDH (units/L) | 0-271 | 1139 | | | | | | | |
| SARS-COV-2 PCR | Negative | Positive | Negative | | | | | | |

Abbreviations: IV, intravenous; Pred, prednisone; q.o.d, every other day regimen; hctz, hydrochlorothiazide; RBC, red blood cell; hpf, high-power field; CRP, C-reactive protein; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; iHD, Intermittent hemodialyses.

**Table 2.** Summary of Serologies and Infectious Workup.

| Measure | Result | Reference |
|---|---|---|
| ANA | Negative | Negative |
| Cytoplasmic C-ANCA | <1:40 | <1:40 |
| Perinuclear P-ANCA | <1:40 | <1:40 |
| Anti-GBM | Negative | Negative |
| Cryoglobulin | Negative | Negative |
| C3 | 112 | 81-157 mg/dL |
| C4 | 28 | 12-39 mg/dL |
| Hepatitis B core antibody | Negative | Negative |
| Hepatitis B surface antigen | Negative | Negative |
| Hepatitis C antibody | Negative | Negative |
| HIV antigen and antibody | Nonreactive | Nonreactive |
| EPV | Negative | Negative |
| CMV DNA PCR | <137 | <137 IU/mL |
| Parovirus | <100 | <100 copies/mL |
| Adenovirus | Negative | Negative |
| QuantiFERON Gold test | Negative | Negative |
| Blastomyces antibody | Negative | Negative |
| Histoplasma antigen-urine | <0.2 | <0.2 ng/mL |
| Coccidioides antibody | Negative | Negative |
| ACE | <40 | < 40 μg/L |

Abbreviations: ANA, antinuclear antibody; ANCA, anti-neutrophilic cytoplasmic autoantibody; anti-GBM, anti-glomerular basement membrane; C, complement; HIV, human immunodeficiency virus; EBV, Epstein-bar virus; CMV, cytomegalovirus; PCR, polymerase chain reaction; ACE, angiotensin-converting enzyme.

hypertrophy and increased protein reabsorption droplets. The uninvolved glomeruli were largely unremarkable, without crescents, necrosis, or thrombi. There was diffuse acute tubular injury, and focal areas of acute tubular necrosis (ATN) were noted. The interstitium showed severe, diffuse edematous change with a prominent inflammatory infiltrate composed primarily of lymphocytes, plasma cells, and clusters of eosinophils. In addition, focal interstitial granulomas were identified. Immunofluorescence microscopy was negative. Electron microscopy showed extensive foot process effacement (approximately 70%-80%), with focal areas of microvillus transformation. The endothelial areas were remarkable for multiple tubuloreticular inclusions within the endothelial cell cytoplasm (see Figure 1). Additional stains were obtained, and CD163 highlighted histiocytic cells in granulomas. Grocott methenamine silver (GMS) and acid-fast bacillus (AFB) stains were negative.

## Clinical Course

The patient was started on remdesivir and dexamethasone for pulmonary manifestations of COVID-19. However, dexamethasone was stopped early due to minimal pulmonary involvement. After the biopsy results returned, the patient was started on high-dose steroid therapy on day 18. He received pulse dose intravenous (IV) methylprednisone (1000 mg/day for 3 days) followed by 1 mg/kg/day of oral prednisone. The patient remained on dialysis for a total of 22 days. He experienced anxiety, tremulousness, insomnia, and weight gain with high dose of daily prednisone and therefore was transitioned to an every other day regimen on day 63. Losartan/hydrochlorothiazide (losartan/hctz) was added on day 64, and prednisone taper was started on day 77. He was doing very well clinically at the last follow-up visit on day 121, his blood pressure was 119/70, and he was without any edema. He continues on maximally tolerated losartan/hctz with ongoing every other day regimen of prednisone taper with plan to be fully off of steroids by 6 months. Genetic screening for APOL1 high-risk allele was offered to the patient; however, he declined genetic testing.

## Discussion

To our knowledge, this is the first case of COVID-19-Associated Collapsing Glomerulopathy (COVAN) in association with severe granulomatous interstitial nephritis (GIN) reported in the literature. The COVAN is a well-established entity, occurring more commonly among patients with 2 high-risk APOL1 alleles.[1-5] In the largest kidney biopsy series to date on COVID-19 patients (240 native and 44 allograft biopsies), COVAN was the most common diagnosis occurring in 25.8% of native biopsies and 4.5% of allograft biopsies.[3] Acute tubular necrosis is commonly found in COVID-19 and COVAN cases and is often quite severe.[6,7] In contrast, acute interstitial nephritis (AIN) related to COVID-19 has not been commonly described in published kidney biopsy series. Moreover, when it occurs along with COVAN, it is usually mild and focal.[8] A large fraction of patients who present with COVAN present with severe kidney failure requiring dialysis at the time of presentation. The outcomes of these patients are variable although the majority of patients will remain with significant proteinuric chronic kidney disease even if they recover off dialysis.[9] A recent publication by Kudose et al in 2021 followed 23 patients with COVAN over a median of 155 days. The authors found 61% of the patients with COVAN required dialysis at presentation, and 50% of these patients eventually achieved dialysis independence.[10] Despite most patients in this study being off dialysis at end of follow-up, no patient in the study had complete proteinuric remission at the time of study follow-up even with steroid therapy. A larger fraction of patients who received steroid in this study were off dialysis at end of the study follow-up compared with patients who did not receive steroid, but this did not reach statistical significance, and conclusions on the utility of prednisone for COVAN is further limited due to the retrospective observational nature of the study.[10] Our patient was able to come off dialysis with recovery of kidney function back to his previous baseline, and while he did not yet attain a proteinuric remission, his proteinuria markedly improved as well and his serum albumin normalized. Our patient's clinical course seems to have been among the more positive kidney outcomes described

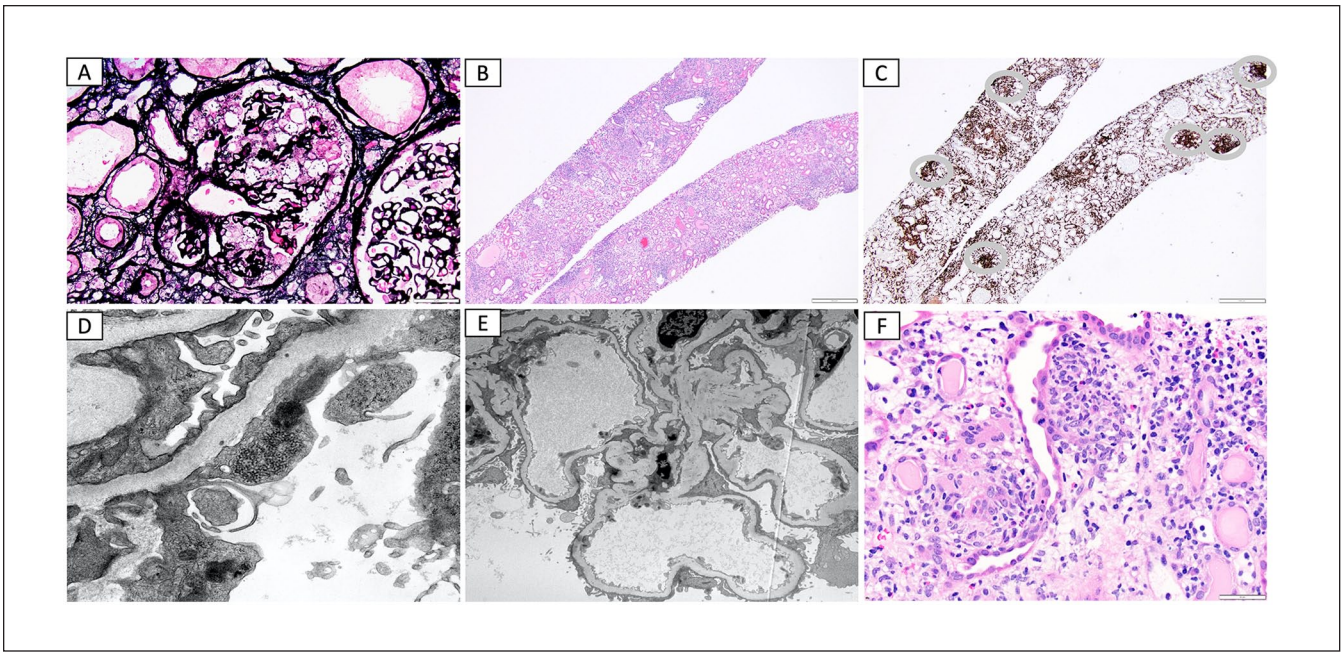


**Figure 1.** (A) Jones Silver Stain at 40× magnification: central glomerulus showing collapse of the glomerular tuft with overlying podocyte hypertrophy, proliferation, and cytoplasmic protein reabsorption droplets. (B) H and E at 2× magnification: low power image of 2 biopsy cores showing multiple granulomas. (C) CD163 immunohistochemical stain (histiocytic marker) showing increased staining of histiocytic cells in the areas of granulomatous inflammation, indicated by the circles. (D) Electron microscopy image at 25 000× magnification: tubuloreticular inclusion in the endothelial cell cytoplasm (center). (E) Electron microscopy at 4000× magnification: diffuse effacement of the podocyte foot processes. (F) H and E at 40× magnification: high power image of 2 granulomas indenting either side of a dilated distal tubule showing a mitotic figure in an epithelial cell. The granuloma on the left shows prominent multinucleated cells and the one on the right shows mixed inflammatory cells. Intense background interstitial inflammation with scattered eosinophils is seen away from the granulomata.
Abbreviation: H and E, hematoxylin and eosin.

among COVAN cases, which in part may be related to the steroid responsiveness of the concomitant GIN lesion.

Granulomatous interstitial nephritis is a rare histologic diagnosis present in approximately 1% of native kidney biopsies and 0.6% of kidney transplant biopsies.[11,12] It is associated with medications, infections, sarcoidosis, autoimmune conditions, crystal deposits, paraproteinemia, and granulomatosis with polyangiitis. Implicated medications include anticonvulsants, antibiotics, NSAIDs, allopurinol, proton pump inhibitors, antivirals, bisphosphonates, and diuretics.[11,12] Mycobacterium tuberculosis (and other mycobacterial organisms), fungi, *Brucella* spp., viruses, or parasites are the common infectious culprits associated with GIN.[11,12] In our patient, the usual infectious and systemic conditions associated with GIN were excluded.

Szajek et al report the only described case of GIN in COVID-19 in a critically ill patient with severe acute respiratory distress syndrome and multi-organ failure. The patient developed hemolysis and maculopapular rash, and dialysis-dependent acute kidney injury (AKI). A kidney biopsy revealed GIN without concomitant glomerular injury, and his condition improved with corticosteroid therapy.[13] In our patient's case, we suspect his prior use of NSAIDs contributed to the GIN found on kidney biopsy, and we suspect a significant amount of the AKI was attributed to the GIN lesion. Still, we cannot exclude the possibility that the GIN may have been primed by the acute inflammatory state associated with upregulation of proinflammatory cytokines during the ongoing COVID-19 infection.[8]

## Conclusion

We have presented a rare case of GIN in a patient with COVAN. With negative infectious and autoimmune evaluation, it is possible the GIN was secondary to drug exposure and/or potentiated by the inflammatory milieu of COVID-19 infection. Even several years into the pandemic, we continue to find new kidney pathology among COVID-19 patients. Kidney biopsy was absolutely necessary in this case and informed a dedicated treatment plan that allowed a remarkable recovery of kidney function.

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## Ethics Approval

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

## Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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