A case of crescentic glomerulonephritis in a patient with COVID-19 infection
A case report and literature review

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Abstract
Rationale: Kidney involvement with COVID-19 infection is a well-known complication, and the majority of kidney involvement is related to ischemic injury/acute tubular injury. However, there are some cases of glomerulonephritis, the etiology of which is not yet known, but an immune process is likely to be the trigger.

Patient concerns: A 27-year-old man presented to our hospital with facial puffiness and lower-limb swelling.

Diagnosis: Laboratory assessment revealed features of impaired kidney function with proteinuria and hematuria; COVID-19 polymerase chain reaction was positive, which was consistent with pauci-immune crescentic focal segmental glomerulonephritis.

Intervention: After renal biopsy, the patient was started on methylprednisolone and rituximab. Due to worsening kidney parameters, he underwent intermittent hemodialysis as needed.

Outcome: Kidney function tests partially improved; he was discharged on oral steroids with follow-up in the nephrology clinic to observe for the need for further hemodialysis.

Lessons: We conducted a literature review of cases of glomerulonephritis associated with COVID-19 and described numerous types of glomerulonephritis. This report highlights the importance of recognizing emerging glomerulonephritis with COVID-19, the different pathological patterns of renal biopsies, and management interventions and responses.

Abbreviations: AKI = acute kidney injury, ANCA = antineutrophilic cytoplasmic antibodies, anti-GBM = anti-glomerular basement membrane, APOL1 = Apolipoprotein L1 gene, FSGS = focal segmental glomerulosclerosis, GN = glomerulonephritis. HbsAg = hepatitis B surface antigen, HCV Ab = hepatitis C antibodies, HIV Ag/Ab = human immunodeficiency virus antigen/antibody combo test, PCR = polymerase chain reaction.

Keywords: acute kidney injury (AKI), antineutrophilic cytoplasmic antibodies (ANCA), COVID-19 infection, focal segmental glomerulosclerosis (FSGS), glomerulonephritis (GN)

1. Introduction
The COVID 19 pandemic has evolved and spread globally by 2020, affecting millions of people, with primary involvement of the respiratory system and a wide range of systemic involvements have been observed too.[1] Kidney involvement is a well-established finding associated with COVID infection.[1,2] Multiple mechanisms contribute to acute kidney injury, including infectious, immune-mediated, thrombotic, or toxic mechanisms.[3] with only a few case reports of COVID 19 infection with glomerulonephritis,[4] especially collapsing glomerulonephritis.[5] Here, we report a case of pauciimmune crescentic glomerulonephritis in a patient with COVID 19 infection that responded partially to steroids and rituximab. In a review of the literature, 24 cases of glomerulonephritis associated with COVID-19 were reviewed. Of these patients, 91% (22/24) underwent kidney biopsy, and collapsing FSGS was the most common type of glomerulonephritis (62.5%). Most patients were treated with immunomodulator therapy. The outcome was variable, with 45.8% of the patients remaining dialysis-dependent.

2. Case presentation
A 27-year-old male of Asian descent with no past medical history presented to the emergency department with facial puffiness and...
lower limb swelling. It started 5 days earlier and gradually worsened. He did not complain of fever, chills, cough, shortness of breath, or hemoptysis. It was not associated with a decrease in urine volume or change in urine color. He denied a recent history of pharyngitis, skin infection, or intake of nonsteroidal anti-inflammatory drugs. He had no family history of kidney or autoimmune diseases.

On examination, the patient had lower limb edema with puffiness around the eye. His blood pressure was 155/89 mm Hg, heart rate was 75 bpm, temperature was 36.9°C, and oxygen saturation was 98%. His basic laboratory works up showed white blood cells count 10.2 × 10^9/L, hemoglobin 8.1 g/dL, hematocrit 25.1%, mean corpuscle volume 90.9 femtoliter, platelets 184 × 10^9/L. His blood urea level was elevated to 109.2 mg/dL, serum creatinine 6.06 mg/dL. His serum electrolyte, potassium, and bicarbonate levels were 142 mEq/L, raised serum potassium 6.2 mEq/L, bicarbonate 17.7 mEq/L. His C-reactive protein was 3.3 mg/L with a lactate dehydrogenase level of 363 U/L. The patient’s urine protein ratio was high 665 mg/mmol. Urine analysis showed urine protein +3 and urine blood +3. Ultrasonography of the kidneys showed increased echogenicity, good corticomedullary differentiation, and trace perinephric free fluid.

A detailed work-up for acute kidney injury (AKI) was performed after consultation with the nephrology team. HIV Ag/Ab, HbsAg, HCV Ab, antinuclear antibodies, anti-GBM, and ANCA tests were all negative. His serum complement C4 level was normal. The serum complement C3 level was mildly low 0.87 a reference range (0.90 of 1.80). COVID-19 PCR was performed as a routine admission requirement and returned positive results. He was transferred to a COVID specialized facility where he was treated conservatively for COVID infection. He did not require antiviral drugs, such as remdesivir.

The patient underwent a kidney biopsy on the third day of admission, which was complicated by hematoma, and was treated conservatively. The patient underwent an emergency session of hemodialysis via the central line due to fluid overload and worsening renal parameters on the sixth day of admission, and was then placed on hemodialysis based on need.

Renal biopsy results were obtained on the eighth day, and no preliminary reports were provided. Biopsy revealed cortico-medullary tissue with 6 glomeruli, 2 of which were globally sclerosed, and 2 showed segmental sclerosis with mesangial matrix expansion, mesangial cell proliferation, and focal fibrinoid necrosis with karyorrhexis and crescent formation. The other 2 viable glomeruli showed no significant abnormalities under light microscopy. Mild to moderate focal tubular and interstitial fibrosis (approximately 20–25% of the cortical tissue). There was a mild diffuse interstitial inflammatory infiltrate composed mainly of lymphocytes with occasional eosinophils. One medium-sized artery was thickened, with moderate subintimal fibrosis, medial hypertrophy, and focal mucoid changes. The arterioles were within normal limits. Indirect immunofluorescence microscopy of the biopsy specimen revealed mild, fine granular mesangial deposits with IgA and IgM (1+ for each). IgG, complement components C3 and C1q, and fibrinogen tests were negative. The biopsy report was diagnostic for pauci-immune focal and segmental glomerulonephritis with crescent formation. (Figs. 1, 2 and 3). We discussed the results with the pathologist, and IgA and IgM positivity was found in 60% of Pauci-immune cases. Although Pauci-immune crescentic glomerulonephritis with severe inflammation often shows positive findings for fibrinogen, in our case it was found to be negative, possibly due to the small biopsy volume, and only 2 glomeruli showed fibrinoid necrosis; repeated immunofluorescence showed the same findings—weak positivity of IgA and IgM, and negative for fibrinogen (Fig. 4).

The patient was treated with methylprednisolone 500 mg IV for 3 days and then received 1 dose of rituximab (1000 mg IV). His kidney function partially improved. Oral prednisone (60 mg) was administered once daily. The patient underwent intermittent hemodialysis as needed. After stabilization, the patient was discharged home on oral prednisone 60 mg once daily for months.
with outpatient follow-up in the nephrology clinic to taper down the steroids. The patient was scheduled to receive another dose of rituximab 2 weeks after the first dose. Upon discharge, his creatinine and urea levels were 3.1 mg/dL, urea 82.2 mg/dL.

3. Discussion

COVID-related kidney involvement is now a well-recognized manifestation of COVID-19. Multiple mechanisms, including cytotoxic injury due to direct viral invasion, acute tubular necrosis, thrombotic microangiopathy induced by a procoagulant state, and immune-mediated response derived from a cytokine storm. Probably immunological processes are probably the leading mechanisms for the development of glomerulonephritis. The characteristics of the reported cases of glomerulonephritis are shown in Table 1.

Our patient presented with symptoms of fluid overload that developed over a week. Although he had no history of kidney
disease and his renal function test results were within the normal range 9 months ago, we cannot exclude the possibility of an underlying kidney disease. The presentation of the reported cases varies from respiratory involvement to symptoms related to kidney injury, and some have very vague systemic symptoms. In our case, the patient was found to have nephrotic range proteinuria and microscopic hematuria, and all cases in Table 1 had proteinuria ranging from subnephrotic range to nephrotic with variable hematuria, which is related to different types of manifesting glomerulonephritis.

Renal biopsy was the most common type of GN in 91% of the total cases with collapsing glomerulonephritis (62.5%), a subtype of focal segmental glomerulosclerosis [5,6,8]. Collapsing FSGS is more common in HIV-infected patients [5,9]. The kidney biopsy of our patient showed crescentic glomerulonephritis, which was previously reported as a COVID-19 infection [10]. Other types of glomerulonephritis-like necrotizing glomerulonephritis have also been reported [11]. To note that case numbered 7 (Table 1) had IgA nephropathy before COVID infection. Some cases mentioned in the table (cases 4 and 5) did not undergo biopsy.

### Table 1: Characteristic of reported glomerulonephritis associated with COVID infection.

| # | Author | Year | Age | Gender | Race | Co-morbidities | Presentation | Serum Cr | Proteinuria | Hematuria | Imaging | Immunology | Biopsy | Treatment | Outcome |
|---|--------|------|-----|--------|------|----------------|-------------|----------|------------|-----------|---------|------------|--------|-----------|---------|
| 1 | Uppal  | 2020 | 64  | Male   | Black| Cryptogenic organizing pneumonia | Shortness of breath | 7.97 mg/dL | Present | Not available | p-ANCA, ANA | p-ANCA | Crescentic glomerulonephritis | Glucocorticoids, rituximab | Improved |
| 2 | Uppal  | 2020 | 46  | Male   | South Asian | Diabetes | Fever, diffuse purpuric rash | 2.9 mg/dL | Present | Not available | c-ANCA | c-ANCA | Focal necrotizing glomerulonephritis | Glucocorticoids, rituximab | Improved |
| 3 | Meenakrishnan  | 2020 | 25  | Male   | Not available | NA | Renal failure, anuria, portal blood flow | 3.7 mg/dL | Present | Not available | c-ANCA | c-ANCA | Crescentic glomerulonephritis | Glucocorticoids, rituximab | Improved |
| 4 | Shah   | 2020 | 18  | Male   | Black | Asthma | Vomiting, diarrhea, facial swelling | 0.32 mg/dL | Present | Not available | – | – | – | Not done | Improved |
| 5 | Akarade | 2020 | 15  | Male   | Not available | NA | Fever, generalized edema, and oliguria | 0.35 mg/dL | Present | Not present | ANA, C4 | – | – | Glucocorticoids | Improved |
| 6 | Pérez   | 2020 | 88  | Male   | Black | Hypertension, DM, kidney failure | Shortness of breath | 7.87 mg/dL | Present | Present | Not available | p-ANCA, ANA | Crescentic glomerulonephritis | Glucocorticoids and angiotensin II receptor blocker | Improved, HD dependent |
| 7 | Malhotra | 2020 | 64  | Male   | Black | Hypertension, DM, CKD II | Shortness of breath, fever | 2.3 mg/dL | Present | Present | Not available | – | Collapsing FSGS | Glucocorticoid | Improved, HD dependent |
| 8 | Deshmukh | 2020 | 42  | Male   | South Asian | NA | Fever, cough, shortness of breath | 1 mg/dL | Present | Present | Not available | – | Collapsing FSGS | Angiotensin converting enzyme inhibitors, intravenous antibiotics, HD | Lost follow up |
| 9 | Deshmukh | 2020 | 54  | Male   | Black | Hypertension, DM, CKD II | Fever, cough, loss of smell | 6.51 mg/dL | Present | Present | Unremarkable | – | Collapsing FSGS | Glucocorticoid, MMF, tacrolimus | HD dependent |
| 10 | Deshmukh | 2020 | 45  | Male   | Black | DM, kidney transplant | Postural hypotension | 4.87 mg/dL | Present | Present | Unremarkable | – | Collapsing FSGS | Glucocorticoid, MMF, tacrolimus | Improved |
| 11 | Lazarov | 2020 | 29  | Male   | Black | Kidney transplant | Fever, cough, vomiting | 6.04 mg/dL | Present | Present | Not present | – | Collapsing FSGS | Glucocorticoid, MMF, tacrolimus | Improved |
| 12 | Kissing  | 2020 | 63  | Male   | Black | Hypertension | Fever, shortness of breath | 1.2 mg/dL | Present | Not present | Not available | – | Collapsing FSGS | Angiotensin converting enzyme inhibitors, intravenous antibiotics, HD | Not available, antibiotics, HD | Improved |
| 13 | Lusier  | 2020 | 44  | Female | Female | Hypertension, DM, CKD II | Fever, cough, vomiting, flank pain | 4 mg/dL | Present | Present | Unremarkable | Anti SSA, AANA | Active necrotizing glomerulonephritis | Glucocorticoids, rituximab | Improved |
| 14 | Pérez   | 2020 | 46  | Male   | Black | Obesity, obstructive sleep apnea | Abdominal pain, nausea, decreased UOP | 12.5 mg/dL | Present | Not present | t-echogenicity | – | Collapsing FSGS | Glucocorticoid | HD dependent |
| 15 | Basrithin | 2021 | 17  | Male   | Not available | NA | Decrease in urine output, nausea, vomiting, fever, oliguria, dark urine | 10.8 mg/dL | Present | Present | t-echogenicity | – | Active necrotizing glomerulonephritis | Glucocorticoids, rituximab | HD dependent |
| 16 | Basrithin | 2021 | 16  | Male   | Not available | NA | Fever, cough, shortness of breath | 15.5 mg/dL | Present | Present | Not available | – | Collapsing FSGS | Proximal tubulointerstitial nephritis | Improved |
| 17 | Magon  | 2020 | 28  | Female | Black | Asthma | Fever, cough, shortness of breath | 6.5 mg/dL | Present | Present | Unremarkable | – | Collapsing FSGS | Glucocorticoids | HD |
| 18 | Magon   | 2021 | 55  | Male   | Black | HTN, CKD II | Fever, cough, vomiting | 3.17 mg/dL | Present | Present | 2 present | t-echogenicity | Collapsing FSGS | Glucocorticoids | Improved, lost follow up |
| 19 | Wu      | 2020 | 55  | Male   | All black | HTN, CKD II | Fever, cough, vomiting | 6.5 mg/dL | Present | Present | Unremarkable | – | Collapsing FSGS | Glucocorticoids | Improved |

ANA = antinuclear antibodies, c-ANCA = proteinase 3 antineutrophilic cytoplasmic antibodies, CKD = chronic kidney disease, Cr = creatinine, F = female, HD = hemodialysis, HTN = hypertension, M = male, NA = not applicable, p-ANCA = myeloperoxidase antineutrophilic cytoplasmic antibodies, RF = rheumatoid factor, SSA = anti-Sjögren’s syndrome-related antigen A autoantibodies.
as they were young and presented with nephrotic syndrome symptoms. They were presumed to be minimal change diseases and responded well to glucocorticoids.\textsuperscript{[13,14]}

The immunologic workup was positive in several cases.\textsuperscript{[7,16,17]}
However, in our case, the workup was negative, including ANCA. Depending on this and renal biopsy results, he was labeled as ANCA-negative Pauci-Immun Glomerulonephritis. Similar to all glomerulonephritis cases, our patient was treated with intravenous methylprednisolone for 3 days with 1 dose of rituximab. The patient required intermittent hemodialysis sessions because of worsening volume overload.

The prognosis in such cases varies from partial improvement in renal function to full dependence on regular dialysis. This may be related to the severity of acute kidney injury, underlying kidney disease, or other comorbidities. Our patient responded partially to the treatment and was discharged on oral prednisolone with a tapering regime and was scheduled to receive second dose of rituximab as an outpatient. However, his Cr level did not return to normal ranges, which can be attributed to a preexisting kidney disease. However, another possibility is that the patient had a post-biopsy hematoma and required multiple abdominal CT scans with contrast to follow-up the hematoma size. It is not yet clear whether the patient will undergo regular renal replacement therapy. Thus far, 46% of the reported cases have become dependent on hemodialysis.

4. Conclusion

Acute kidney injury can occur in COVID-related infections, and the most common cause is collapsing glomerulonephritis. However, crescentic glomerulonephritis is also associated with COVID-19, as in our case. We report this case with a literature review to highlight the different types of glomerulonephritis associated with COVID-19. It is also reasonable to perform renal biopsy in patients with suspected glomerular injuries. We hope that the publication of such data will give us more insight into the disease, risk factors, and interventions, such as medications, early or delayed renal replacement therapy, and prognosis.

Acknowledgments

The authors acknowledge the internal medicine residency program for their motivation and support.

Author contributions

Dr. Mouhammad J Alawad and Dr. Ijaz Kamal wrote and edited the manuscript; Dr. Eihab A Subahi and Dr. Haneen A Al-Ani were responsible for literature review. Dr. Noheir M. Taha provided us with the pathological images and interpretations. All authors approved the final manuscript.

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