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Multicenter Clinicopathologic Correlation of Kidney Biopsies

Performed in COVID-19 Patients Presenting With Acute Kidney Injury or Proteinuria

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Abstract
Rationale and Objective: Kidney biopsy data inform us about pathologic processes associated with SARS CoV-2 infection. We conducted a multi-center evaluation of kidney biopsy findings in living patients to identify various kidney disease pathology in patients with COVID-19 and their association with SARS-CoV-2 infection.

Study Design: Case series.

Setting and Participants: We identified 14 native and 3 transplant kidney biopsies performed for-cause in patients with documented recent or concurrent COVID-19 infection treated at 7 large hospital systems in the United States.

Observations: Males and females were equally represented in our study cohort, with a higher proportion of Black (n=8) and Hispanic (n=5) patients. All 17 patients had RT-PCR confirmed COVID-19 infection, but only 3 presented with severe COVID-19 symptoms. Acute kidney injury (AKI; n=15) and proteinuria (n=11) were the most common indications for biopsy and these symptoms developed concurrently or within 1 week of COVID-19 symptoms in all patients. Acute tubular injury (n=14), collapsing glomerulopathy (n=7) and endothelial injury/thrombotic microangiopathy (n=6) were the most common histologic findings. Two of the three transplant patients developed active antibody-mediated rejection weeks after COVID-19 infection. Eight patients required dialysis, but others improved with conservative management.

Limitations: Small study size and short clinical follow up.

Conclusions: Cases of even symptomatically mild COVID-19 infection were accompanied by AKI and/or heavy proteinuria that prompted a diagnostic kidney biopsy. While acute tubular injury was seen among the majority of them, uncommon pathology such as collapsing glomerulopathy and acute endothelial injury were detected, and most of these patients progressed to irreversible kidney injury and dialysis.
Index Words

Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), acute kidney injury (AKI), renal complications of COVID-19, collapsing glomerulopathy, thrombotic microangiopathy, kidney biopsy, allograft biopsy, antibody-mediated rejection, renal pathology, case series
Plain Language Summary

Acute kidney injury is common in patients with COVID-19 disease. We undertook a multi-center study to evaluate kidney biopsy findings in living patients to identify different kidney disease pathology in COVID-19 patients. Most patients in our cohort developed acute kidney injury concurrent with mild COVID-19 symptoms. Acute kidney injury (AKI) and proteinuria were the most common indications for biopsy. Both common and rare pathological processes such as acute tubular injury, collapsing glomerulopathy, and endothelial injury/thrombotic microangiopathy were the most common histologic findings. Two of the three transplant patients developed active antibody-mediated rejection weeks after COVID-19 infection. These data suggest that even symptomatically mild COVID-19 infection can be associated with AKI and/or heavy proteinuria and may warrant diagnostic kidney biopsy.
Introduction

Since its identification, SARS-CoV-2 infection and its resulting disease, COVID-19, has grown into a worldwide pandemic with devastating medical and financial impacts. Though the primary targets of injury are the lungs and airways, cardiac and renal involvement are common and portend a worse prognosis.\(^1\)\(^–\)\(^4\) Pre-existing renal disease or diseases known to contribute to renal impairment such as hypertension and diabetes are risk factors for an aggressive clinical course.\(^2\)\(^,\)\(^5\)\(^–\)\(^8\) \textit{De novo} renal impairment in SARS-CoV-2 infected patients manifests as acute kidney injury (AKI), proteinuria, and hematuria.\(^3\)\(^,\)\(^9\) Various mechanisms have been proposed for kidney injury, including ischemia related to severe pulmonary injury, high levels of circulating pro-inflammatory cytokines (“cytokine storm”) and bradykinin, and possible direct infection of the renal parenchyma by SARS-CoV-2. However, very few patients with COVID-19 undergo kidney biopsy to identify the pathologic processes affecting the kidney, since management of pulmonary disease and infection precautions often take precedence. Therefore, we aggregated kidney biopsies performed on patients with documented COVID-19 from multiple large medical centers in the United States to identify clinicopathologic correlations of renal impairment.

Methods

\textit{Identification of kidney biopsies of patients with COVID-19 infection}

After study conception by SA, NKA and KDS, a request for collaboration and case contribution was sent to renal pathologists at large medical centers. Once cases were identified at each institution, biopsy and electronic health record review were performed locally as human subjects exempt research with the approval of waiver of consent by local institutional review boards: University of Washington (6 cases; STUDY00010368), Oregon Health Sciences University (2
cases; STUDY0017467), Cedars-Sinai Medical Center (3 cases; STUDY0000903); University of Chicago (1 case; IRB20-1260), University of Arizona (2 cases; Protocol 2005664752), Stanford University (1 case; IRB 43782) and University of California Los Angeles (UCLA, 2 cases; IRB 20-001635).

**APOL1 genotyping**

For case 1, genetic testing was performed at GeneDx Laboratories (Gaithersburg, MD). For case 6, genomic DNA was isolated from EDTA anticoagulated blood with the PureLink Genomic DNA kit (ThermoFisher Scientific). The region of APOL1 containing the G1 and G2 risk alleles was amplified by PCR, and the product sequenced by automated sequencing in 2 reactions. Sequence data were analyzed by the most recent version of the Mutation Surveyor software (SoftGenetics).

**Immunohistochemistry and in situ hybridization for SARS-CoV-2**

For SARS-CoV-2 nucleocapsid protein, formalin-fixed paraffin-embedded (FFPE) tissue sections were immunohistochemically stained with an antibody to SARS-CoV nucleocapsid protein (Catalog #40143-T62, Sinobiological, Wayne, PA) at 1:2000 dilution on Leica Bond III instruments after 20 min antigen retrieval with epitope retrieval 2, followed by Leica Bond Polymer Refine detection chemistry. For RNA in situ hybridization, FFPE was stained with SARS-CoV2 probe (ACD Bio RNAscope® Probe - V-nCoV2019-S, cat# 848568) on Leica platform with 3,3’-diaminobenzidine (DAB), protease retrieval, and hybridization per manufacturer protocols.

**Results**

**Clinical presentation**
We identified 17 patients (8 male, 9 female) with RT-PCR documented COVID-19 infection. The clinical characteristics of our cohort are summarized in Table 1. Additional information on baseline laboratory and clinical parameters, medication usage and pathologic findings are detailed in Table S1. The median age of our patients was 54 years (range 34-77 years). Our cohort was predominantly Black (n= 8, 47%) and Hispanic (n= 5, 29%). Most patients had only mild COVID-19 related symptoms such as upper respiratory tract infection, cough, fatigue or low-grade fevers, though at least three required hospitalization for hypoxic pulmonary failure. Fourteen patients presented with native kidney impairment while three presented with allograft kidney impairment. AKI (n=15; median serum creatinine 5.5 mg/dL and range 0.7-12 mg/dL) and heavy proteinuria (n=11) were the most common indications for biopsy. Hypertension was almost uniformly present in our patient cohort, while diabetes and obesity were less frequent.

The most severe AKI presentations were in the six patients who presented with severe hypertension often >150/100 mmHg (cases 6-11). Four of these (cases 8-11) had characteristic laboratory features of thrombotic microangiopathy (TMA), including anemia, thrombocytopenia, elevated serum lactate dehydrogenase, and low haptoglobulin with normal ADAMTS13 activity. Three of 4 had additional conditions which may have contributed to TMA, including cytotoxic and/or illicit drug use and poorly controlled hypertension. The first of these patients (case 8) presented with mental status changes and intracranial hemorrhage and ultrasound imaging revealed atrophic appearing kidneys suggesting long-standing poorly controlled blood pressure. The second patient (case 9) had mental status changes, normal complement levels, and had previously been treated with gemcitabine for adenocarcinoma. She presented with oliguric AKI and nephrotic range proteinuria. The third patient (case 10) had evidence of activation of the alternative complement pathway (low serum C3 with normal C4), which has been reported in
patients with COVID-19. The fourth patient initially presented only with fatigue (case 11) and 2 days later he was diagnosed with COVID-19. At that time his serum creatinine was 1.62 mg/dL. 23 days later, his pulmonary symptoms had worsened, and he was admitted for pulmonary edema and high blood pressure (165/87 mmHg). His social history was significant for active cocaine use and he was being treated with gemcitabine, vinorelbine, and doxorubicin for primary refractory classical Hodgkin lymphoma (first diagnosed 2017 status post multiple cycles of chemotherapy with failure and progression). His serum creatinine was 3.9 mg/dl on day of admission to hospital and he had evidence of hemolytic anemia (Hgb: 8.6; Hct 27%; 2+ shistocytes on blood smear; aPTT 22.7 sec; fibrinogen activity 180 mg/dL; D-dimer 7,546).

For the kidney transplant recipients, case 15’s original cause of renal failure was focal and segmental glomerulosclerosis (FSGS) in the setting of HIV infection. She received a deceased donor allograft in 2015. Her post-transplant course was complicated by acute vascular rejection approximately 10 months after transplantation. The patient was out of state when she was hospitalized with a 4-day history of COVID-19 symptoms and elevated serum creatinine (baseline 1.1 mg/dL). She eventually recovered without requiring intubation. Upon return to her home state and follow up with her transplant nephrologist, her serum creatinine was found to be persistently elevated with the appearance of several new high titer donor-specific antibodies. This prompted a kidney biopsy and initiation of treatment for antibody-mediated rejection after the report was returned.

Case 16’s original cause of renal failure was unknown, presumed due to undiagnosed hypertension or calculi. He received a deceased donor allograft in 2000 and his post-transplant course was relatively uncomplicated without any biopsy-diagnosed episodes of rejection. In 2019, he presented with elevated serum creatinine rising from his baseline of 1.5 to 2.2 mg/dL.
and increasing proteinuria (3 g). At that time, he was biopsy diagnosed with chronic transplant glomerulopathy with negative C4d, focal glomerulitis (g2) and in the setting of a low positive DQ titer. In spring of 2020, the patient presented with progressive hypoxemia requiring up to 4L/min oxygen via nasal canula (he never required intubation) and acute kidney injury. At this time, his FK506 and mycophenolate mofetil (MMF) were held and he was maintained on 10mg/day prednisone till he was stable enough to be biopsied approximately 6 weeks after COVID-19 symptom onset.

Patient #17 had ESKD due to FSGS, and he received a living related kidney transplant 19 months prior; his post-transplant course had been uncomplicated. He developed AKI in the setting of mild COVID-19 symptoms and tested positive for SARS-CoV-2.

There was often a delay between onset of kidney symptoms/COVID-19 diagnosis and performance of the kidney biopsy. Reasons for this delay were varied but included abundance of caution with infectious precautions at the onset of the pandemic (cases 5, 9, 16, 17), hemodynamic instability (cases 1, 8), observation during initial improvement which was followed by further decline (cases 2, 3, 11) and scheduling hurdles (cases 12, 15). These delays were not unique to a given institution and are likely comparable to biopsy-scheduling practices at large referral centers nation-wide.

**Pathologic findings**

**Native Biopsies**

The findings on kidney biopsy are summarized in Table 2 with clinical follow up summarized in Table 3. Clinically, 15 out of 17 patients presented with an acute rise in serum creatinine and 13 of these patients demonstrated histologic evidence of acute tubular injury in their biopsy (Fig
Eleven patients demonstrated focal and segmental glomerulosclerosis (FSGS), which in 7 patients assumed the form of collapsing glomerulopathy (Fig 1B-D). One of these patients (case 6) was diagnosed with collapsing glomerulopathy three years prior and had been clinically stable with a baseline serum creatinine of 2 mg/dL and a urine protein/creatinine ratio of 2 g/g. During the course of his COVID-19 infection, his serum creatinine rose to 12 mg/dL with a 11.4 g/g protein/creatinine ratio. All 11 FSGS patients, as well as the patient diagnosed with minimal change disease (case 5) presented with >3 g/g proteinuria (uPCR), which correlated with diffuse podocyte foot process effacement by electron microscopy. Two patients were tested and found to have high-risk APOL1 genotypes (cases 1 & 6).

Six patients (cases 6-11) demonstrated evidence of acute endothelial cell injury by light and/or electron microscopy including all 4 clinically suspected of having acute TMA (cases 8-11). This ranged from mild injury with ultrastructural evidence of glomerular subendothelial space widening and/or loss of endothelial cell fenestrae to severe injury manifest by endothelial cell swelling and fibrin thrombi within glomerular hilar arterioles and small arteries evident by light microscopy (Fig 1D-F). Peritubular capillary thrombi were not seen in any of the cases in our cohort. Microangiopathic features were seen in the setting of collapsing glomerulopathy (cases 6-9), and/or with prominent arteriolar involvement in the background of severe hypertension (cases 8-11). Additional findings of acute interstitial nephritis, IgA nephropathy, mesangial immune complex deposition of uncertain significance, monoclonal gammopathy (later diagnosed as Waldenstrom’s macroglobulinemia), post-infectious glomerulonephritis, minimal change disease and diabetic nephropathy were also identified (cases 3, 5, 12, 13, 14, 15).

Allograft Biopsies
Two of the three transplant patients (cases 15 & 16) demonstrated microvascular inflammation and positive C4d staining in peritubular capillaries in association with elevated donor-specific antibodies, meeting Banff criteria for active antibody-mediated rejection. The discovery of IgA nephropathy in case 16 was considered incidental de novo disease since the patient’s original cause of ESRD 20 years prior was considered to be due to hypertension/calculi. The glomeruli in this case showed mild mesangial expansion and focal mesangial hypercellularity, but these findings could also be attributed to chronic and active antibody-mediated rejection. A third allograft biopsy (case 17) showed acute tubular injury, and the patient’s creatinine returned to baseline shortly after the biopsy.

Lack of evidence for direct infection of the kidney by SARS-CoV-2

Using electron microscopy, earlier reports have suggested direct viral infection of the kidney.\textsuperscript{11,12} However, unambiguous identification of viral particles in autopsy tissue is difficult due to post-mortem degradation artifacts. We therefore reasoned that 3 criteria were required to establish direct viral infection of tissues: 1) viral particles of expected size (80-140nm) with the electron dense dots of the nucleocapsid cores and, when visible, spikes facing the lumen of vacuoles;\textsuperscript{13,14} 2) viral particles present in the appropriate subcellular compartment (e.g. intracisternal spaces of the endoplasmic reticulum and Golgi, cytoplasmic vesicles, and extracellular spaces) compatible with known viral replication and trafficking pathways;\textsuperscript{15} and 3) orthogonal validation by immunohistochemistry or RNA-ISH (with appropriate clinical validation and controls). These criteria were not met in any of our cases and therefore, we could not establish direct viral infection of the kidney in our cohort. Viral particles were not identified by ultrastructural examination in any of our cases. Electron microscopy revealed intracellular vesicular structures.
with diameters of ~100nm, which by consensus expert opinion represented normal cytoplasmic organelles (e.g., clathrin coated vesicles and multivesicular bodies) and not true viral particles. In addition, immunohistochemistry for SARS-CoV-2 nucleocapsid and RNA in situ hybridization for viral genomes were negative for all 4 patient samples on which it was performed (cases 1, 5, 10, 12).

**Clinical outcome and follow up**

There were often several weeks of delay between kidney impairment onset and the biopsy procedure, and most patients were SARS-CoV-2 PCR negative at the time of biopsy (Table 3). Since most patients had only mild COVID-19 related symptoms, treatment focused on managing their kidney disease diagnosed on biopsy, usually with diuretics and blood pressure control. This resulted in improvement in 7/12 patients; at least eight patients required dialysis including 6/7 patients diagnosed with collapsing glomerulopathy, and all 6 with presenting with suspected or clinically confirmed TMA. Seven patients remain on dialysis at the time of this writing.

**Discussion**

In our cohort of COVID-19 patients, the most frequent indications for biopsy was an acute rise in the serum creatinine (15/17, 88%), new onset of proteinuria (11/17, 65%) and hematuria (4/17, 24%). All patients’ renal dysfunction presented concurrently with or within one week of RT-PCR confirmed SARS-CoV-2 infection, and most had only mild COVID-19 symptoms. However, there was often several weeks delay between onset of COVID-19 symptoms or confirmed positive RT-PCR test and the kidney biopsy procedure (Table 3). Therefore, most biopsies were performed after individuals were PCR-negative and considered to be of low
infection risk. Histologically, acute tubular injury was seen in the majority (14/17, 82%) of our biopsy cohort. The most striking finding is the high incidence of collapsing glomerulopathy (7/17, 41%), which has been reported by multiple groups in association with SARS-CoV-2 infection.\textsuperscript{16–20} The mechanism driving this acute glomerular injury process is possibly related to interferon production, a known trigger of collapsing glomerulopathy.\textsuperscript{21–23} It is less likely that direct podocyte infection is an etiologic factor as the 3/4 patients who were negative for virus by IHC and/or \textit{in situ} hybridization had podocytopathies (1 each FSGS, collapsing glomerulopathy and minimal change disease). We were able to genotype one Black patient (case 1) who was found to carry the high risk G1/G1 \textit{APOL1} genotype. While we did not genotype the other patients in our cohort, 6/7 patients with collapsing glomerulopathy were Black, consistent with other reports demonstrating a strong association between collapsing glomerulopathy in the setting of SARS-CoV-2 infection with high-risk \textit{APOL1} genotypes,\textsuperscript{17,19,24} a susceptibility that parallels its incidence in HIV-infected patients.\textsuperscript{24,25} The last patient with collapsing glomerulopathy (case 6) was a Hispanic patient from Mexico who was also found to have a high risk G2/G2 \textit{APOL1} genotype even though the prevalence of homozygous high-risk \textit{APOL1} genotypes in mainland Hispanics is 0.1%.\textsuperscript{26}

Acute TMA and more subtle ultrastructural evidence of acute endothelial cell injury were also common findings in our cohort (6/17, 35%). 4/6 of these patients had underlying hypertension, and two had prior or ongoing treatment with gemcitabine (one of which also used cocaine), and thus had potential additional drivers for TMA besides SARS-CoV-2 infection. Four patients’ biopsies with TMA/endothelial injury also demonstrated collapsing glomerulopathy, and two allograft biopsies showed endothelial cell injury in the setting of antibody-mediated rejection. Interestingly, TMA has been associated with collapsing
glomerulopathy, and endothelial injury is the most common manifestation of antibody-mediated rejection. Thus, the frequent finding of acute TMA and more subtle ultrastructural evidence of acute endothelial cell injury appears to be the manifestation of the underlying disease processes in our cohort. Endothelial injury and dysfunction are emerging mechanisms in severe COVID-19, and other groups have suggested that endothelial injury may be a manifestation of SARS-CoV-2 infection and contribute to kidney injury. Our series demonstrates that a broad clinical and pathologic spectrum of acute endothelial injury may exist even in the absence of significant COVID-19-related respiratory symptoms, and some of these changes can be attributed to co-existing diseases. It is possible that SARS-CoV-2 infection may exacerbate clinical situations predisposing to endothelial injury such as hypertension, antibody-mediated rejection, pro-thrombotic states and endothelial toxins. Additional data will be helpful to determine whether this is an important clinical consideration.

To our knowledge, this is the first report of infection-related glomerulonephritis (case 12) in the setting of COVID-19. Infection-related glomerulonephritis is most commonly associated with bacterial infections but has been seen in association with viral infections, such as Parvovirus B19 and influenza virus H1N1. Our patient manifested kidney symptoms 19 days after testing positive for SARS-CoV-2, indicating that the timing of glomerulonephritis fits with the pathogenesis of post-infectious glomerulonephritis. However, this patient also had nodular diabetic nephropathy and a concurrent urinary tract infection (UTI), and it is possible that the UTI was a cause of, or contributor to, the infection-related glomerulonephritis. We also report a case of minimal change disease in a one patient (case 5). In contrast to the Black patient with a high-risk (G1/G1) APOL1 genotype who presented with minimal change disease in a recent report, our patient is White. However, it is well appreciated that minimal change disease may
manifest after viral infections or interferon treatment,\textsuperscript{38–41} therefore representing another pathway by which SARS-CoV-2 infection may trigger a podocytopathy.

Two of the three kidney transplant patients in our cohort developed new DSAs and antibody-mediated rejection weeks after COVID-19 infection, which raises the possibility of immune stimulation of alloantibody production during viral infection.\textsuperscript{42,43} In one of these patients (case 16), immunosuppression was reduced during acute COVID-19 hypoxemia, which may have predisposed to development of antibody-mediated rejection. However, in the other patient (case 15) treatment for antibody-mediated rejection was initiated only after diagnostic kidney biopsy was completed and in the setting of new high-titer anti-HLA*DR53 antibodies. Emergence of \textit{de novo} donor specific antibodies has also been recently been reported in a pediatric heart transplant recipient who was infected with SARS-CoV-2.\textsuperscript{44} Kidney allograft recipients may therefore be at increased risk for developing \textit{de novo} DSAs and active antibody-mediated rejection after SARS-CoV-2 infection.

Direct viral infection of the kidney by SARS-CoV-2 has been proposed as a possible mechanism of kidney injury and is an attractive concept since both podocytes and proximal tubular epithelial cells express high levels of the ACE2 entry receptor.\textsuperscript{11,45–47} We could not establish direct kidney infection by SARS-CoV-2 in our cohort, though a caveat is that there was often a several week delay between diagnosis of COVID-19 and performing the kidney biopsy. We note that the temporal relationship between onset of kidney impairment, COVID-19 symptoms and diagnostic biopsy has not been clearly reported in the previous studies to date.\textsuperscript{10,16,17,20,48} Detectable SARS-CoV-2 may wane quickly with time after the onset of infection similar to SARS-CoV.\textsuperscript{49,50} Therefore, these delays meant that most patients in our cohort may have cleared virus from their kidney and were therefore RT-PCR negative by nasopharyngeal
swab at the time of biopsy. Even with this caveat, most recent biopsy and autopsy case series have concluded that there is no significant SARS-CoV-2 infection of the kidney, which is in contrast to the possibility of direct infection that was reported in two earlier studies. Therefore, our study adds to the accumulating evidence that direct and persistent infection of the kidney by SARS-CoV-2 does not appear to play a significant role in kidney disease in most COVID-19 patients.

Many studies have relied solely on electron microscopy to establish direct viral infection of tissues. However, without orthogonal validation and rigorous controls this approach is problematic since there are many ultrastructural mimics of viral particles. Even in the lung, using validated immunohistochemistry and RNA in situ hybridization, very few cells appear to contain detectable virus. If direct viral infection of the kidney occurs, the lower viral load compared to lung tissue would make ultrastructural identification of exceedingly rare SARS-CoV-2 particles in the kidney improbable amongst the ubiquitous viral mimics. In contrast to the patients in two autopsy series or those in a recent biopsy series, the majority of patients in our cohort had only mild COVID-19 symptoms while presenting with acute kidney injury, heavy proteinuria, and/or severe hypertension. Some diseases detected in our patient cohort may represent diagnoses coincident with COVID-19 disease. On the other hand, the high incidence of typically rare disease processes such as collapsing glomerulopathy and thrombotic microangiopathy raises the possibility of SARS-CoV-2 infection contributed to these injuries, even in the absence of direct infection of the renal parenchyma. Given that the majority of SARS-CoV-2 infected patients exhibit only mild symptoms such as those in our cohort, the incidence of acute kidney injury and proteinuria may rise as the pandemic progresses, and
disproportionately impact more vulnerable populations with pre-existing risk factors for kidney
disease or high-risk APOL1 genotypes.

Supplementary Material

Table S1: Additional information on cases.

Article Information

Authors’ Contributions: Research idea and study design: SA, NKA, KDS; data
acquisition: all authors; data analysis/interpretation: all authors; study supervision: SA, NKA,
KDS. Each author contributed important intellectual content during manuscript drafting or
revision and agrees to be personally accountable for the individual’s own contributions and to
ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one
in which the author was not directly involved, are appropriately investigated and resolved,
including with documentation in the literature if appropriate.

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Figure Legend

Figure 1.

A) Case 7 – ATN, original magnification 400X, Jones methenamine silver
B) Case 7 – Collapsing GN, original magnification 400X, Jones methenamine silver
C) Case 6 – Collapsing GN, original magnification 400X, Jones methenamine silver
D) Case 9 – Collapsing GN and TMA, original magnification 400X, Jones methenamine silver
E) Case 8 – TMA, original magnification 400X, Jones methenamine silver
F) Case 8 – TMA Electron microscopy, original magnification 20,900X
| Case # | Age | Sex | Race/Ethnicity | COVID-19 symptoms | HTN | Diabet es | Serum creatinine at biopsy (mg/dL) | Proteinuria | Hematuria | Additional pertinent labs | Reason for kidney biopsy | Biopsy diagnosis |
|--------|-----|-----|----------------|--------------------|-----|-----------|---------------------------------|-------------|-----------|--------------------------|--------------------------|-----------------|
| 1      | 46  | M   | Black          | Acute respiratory failure | Yes | NA        | 8.7                             | 13.7 g/g uPCR | No        | APOL1 G1/G1              | Nephotic syndrome, AKI   | Collapsing FSGS, ATN |
| 2      | 60  | F   | Black          | None                | Yes | No        | 5.7                             | 21 g/g uPCR  | No        | NA                       | Nephrotic range proteinuria, AKI | Collapsing FSGS, ATN |
| 3      | 58  | F   | Black          | Abdominal pain, weakness, fever | Yes | No        | 10.3                           | 20 g/g uPCR  | No        | NA                       | Nephrotic syndrome, AKI   | Collapsing FSGS, ATN |
| 4      | 59  | M   | Black          | Loss of exercise tolerance, splenomegaly | No | No        | 0.7                             | 11.9 g/g uPCR | Yes       | NA                       | Nephrotic syndrome, AKI   | FSGS, ATN, AIN |
| 5      | 52  | F   | White          | Nephrotic range proteinuria, AKI | No | No        | 20 grams                       | NA          | No        | Leukopenia                | Minimal change disease   |                  |
| 6      | 44  | M   | Hispanic       | Mild upper respiratory symptoms | No | No        | 12                             | 11.4 g/g uPCR | No        | APOL1 G2/G2              | Nephrotic range proteinuria, AKI | Collapsing FSGS, EM evidence of endothelial injury, ATN, TIN |
| 7      | 58  | M   | Black          | Cough, fever, hypoxia | No | No        | 11.3                           | 4 grams      | Yes       | NA                       | Nephrotic range proteinuria, AKI | Collapsing FSGS, TMA, ATN |
| 8      | 47  | M   | Black          | None                | Yes | No        | 6.6 (on dialysis) | 7.6 g/g uPCR | Yes       | Hgb 7.6 (L); Plt 226   | Concern for TMA, AKI     | Arteriolar-prominent TMA, Collapsing FSGS, ATN |
| 9      | 63  | F   | Black          | Fatigue             | No  | No        | 6                              | 20 g/g uPCR  | Yes       | Anemia, thrombocytopenia, negative ANA, normal C3/C4, normal ADAMTS13 | Concern for TMA; oliguric AKI and nephrotic range proteinuria | Arteriolar and glomerular-prominent TMA, collapsing FSGS, ATN |
| 10     | 77  | F   | Hispanic       | None                | Yes | Yes       | 3.99                           | 13.41 g/g uPCR | No        | C3 51 (L); C4 20.0 (nl); Haptoglobin <9 (L); elevated d-dimer; LDH | Concern for TMA, AKI, nephrotic syndrome | Arteriolar-prominent TMA, FSGS, mesangial immune complex deposition, ATN |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |
| 11 | 34 | M | Hispanic | Fatigue, weakness, shortness of breath | Yes | No | 11.4 | 2.1 g/g uPCR | NA | Hgb 8.6 (L), thrombocytopenia, schistocytes, Elevated D-dimer | Concern for TMA | Arteriolar and glomerular-prominent TMA |
| 12 | 69 | F | White | Upper respiratory symptoms | Yes | Yes | 4.0 | 5.7 g/g uPCR | NA | Urinary tract infection, E.coli | Nephrotic range proteinuria, AKI | Post-infectious GN, advanced diabetic nephropathy, ATN |
| 13 | 34 | F | White | Cough and runny nose; no fever | Yes | Yes | 1.26 | 7 g/g uPCR; 2.5 g/24hr | No | NA | Nephrotic syndrome, AKI | Advanced diabetic nephropathy with FSGS, ATN |
| 14 | 67 | F | Hispanic | Hypoxia, fever to 100.4°F | Yes | No | 1.42 | 1+ on UA | Yes | LDH 451 (H); Elevated D-dimer | AKI | ATN with kappa light chain staining bias |
| 15 | 47 | F | Black | Sore throat, nasal congestion, anosmia, cough, malaise, pleuritic chest pain, fever | Yes | No | 1.63 | 2+ on UA | No | DR53 6600 (500) new / DP 3000 (new) / DQ4 1600 (new) B44 800 (300) | AKI in transplant patient | Active AMR |
| 16 | 54 | M | Asian | Acute respiratory failure, fever to 104°F, nausea/vomiting | Yes | Yes | 1.9→5.2 | 3 g/g uPCR | No | Hgb 9.7 (L); Plt 109 (L); anti-phospholipid antibodies negative | AKI, proteinuria, edema in a transplant patient | Chronic active AMR, IgAN, FSGS, possible TMA |
| 17 | 42 | M | Hispanic | Cough, sore throat, anosmia, headache, arthralgia, fever to 100.5°F | Yes | No | 1.27→1.43 | 0.15 g/g uPCR | No | No donor specific antibodies | AKI in a transplant kidney | ATN |

Abbreviations: M=male. F=female. NA=not available. AKI=acute kidney injury. TMA=thrombotic microangiopathy. AMR= Antibody mediated rejection. FSGS=focal segmental glomerulosclerosis. ATN= acute tubular necrosis
Table 2. Kidney biopsy findings in patients with COVID-19 infection

| Case # | Diagnosis | ATN | TMA features | gloms/ global gs/ fsgs (# collapsing)/ IFTA | Chronic vascular disease | IF findings | EM findings |
|--------|-----------|-----|--------------|---------------------------------------------|--------------------------|-------------|-------------|
| 1      | Collapsing FSGS, ATN⁺ | Present | None | 2/3/5% (1)/ 50% | Mild AS | Not performed | Diffuse FPE. No immune deposits. No TRIs. No viral particles |
| 2      | Collapsing FSGS, ATN | Severe | None | 2/3/5% (1)/ 50% | Mod AS | Negative | Segmental FPE. No TRIs. No viral particles |
| 3      | Collapsing FSGS, ATN, AIN⁺ | Severe | None | 2/3/5% (1)/ 50% | Severe AS | Negative | 75% FPE. No TRIs. No viral particles |
| 4      | FSGS, ATN, AIN | Severe | None | 2/3/5% (1)/ 50% | Mod AS, severe arteriolosclerosis | Negative | Diffuse FPE. TRIs present. No viral particles |
| 5      | Minimal change disease | No | None | 2/3/5% (1)/ 50% | Minimal AS | Negative | Diffuse FPE. No TRIs. Probable clathrin coated vesicles in endothelial cells and podocytes |
| 6      | Collapsing FSGS, EM evidence of endothelial injury, ATN, TIN | Present | EM evidence of endothelial injury | 2/3/5% (1)/ 50% | None | Negative | Diffuse FPE. Mild subendothelial space expansion. No TRIs. No viral particles |
| 7      | Collapsing FSGS, TMA, ATN⁺ | Severe | Thrombi in 1 glomerulus and arteriole | 2/3/5% (1)/ 50% | Mild AS | Negative | Diffuse FPE. TRIs present. No viral particles |
| 8      | Arteriolar-prominent TMA, Collapsing FSGS, ATN | Present | Arterial fibrin thrombi, swollen endothelium | 2/3/5% (1)/ 50% | Mod AS | Medulla only | Extensive FPE. Variable subendothelial space expansion. No immune deposits. No TRIs. No viral particles |
| 9      | Arteriolar and glomerular- | Severe | Arterial and glomerular fibrin | 2/3/5% (1)/ 50% | Severe AS | Negative | Diffuse FPE. Endothelial swelling, ischemic wrinkling |
| Case | Disease | Renal biopsy findings | Clinical findings | Remarks |
|------|---------|----------------------|------------------|---------|
| 29   | prominent TMA, FSGS, ATN* | thrombi, segmental GBM duplication | and occasional duplication of GBMs. | |
| 10   | Arteriolar-prominent TMA, FSGS, mesangial immune complex deposition, ATN | Severe | Arteriolar TMA | Segmental granular mesangial & capillary wall staining for polyclonal IgG (2+), IgM (1+), C1q (1+) |
|      | 10/0%/50%/30% | Severe AS | Diffuse FPE. Mesangial immune deposits. No subendothelial expansion. TRIs present. Probable multivesicular bodies in podocytes, no viral particles |
| 11   | Arteriolar and glomerular-prominent TMA | Mild | Arterial and glomerular fibrin thrombi, endothelial swelling, mesangiolysis, GBM duplication | Segmental FPE. Marked subendothelial space expansion and accumulation of flocculent material. Segmental duplication of GBMs |
|      | 11/0%/0%/0% | None | Negative | |
| 12   | Post-infectious GN, advanced diabetic nephropathy, ATN | Severe | None | Subepithelial, paramesangial deposits. Frequent FPE. GBM thickening and mesangial sclerosis No TRIs. No viral particles |
|      | 15/28%/7%/40% | Mod AS, severe AH | Irregular coarse granular glomerular C3 (3+) | |
| 13   | Advanced diabetic nephropathy, ATN | Severe | None | GBM thickening and mesangial sclerosis. No TRIs. No viral particles |
|      | 20/15%/15%/mild to mod | Severe AH | Negative | |
| 14   | ATN* | Present | None | Segmental FPE. No deposits or crystals. No TRIs. No viral particles |
|      | 14/14%/0%/10% | Mild AS | Kappa light chain staining bias in tubular droplets and casts | |
| 15   | Active AMR | No | None | Segmental FPE. No TRIs. No viral particles |
|      | 25/10%/0%/50% | Mod AS, AH | C4d diffusely positive | |
| 16   | Chronic active AMR, IgAN, FSGS, TMA | No | Single arterial thrombus | Subendothelial space expansion. Segmental FPE. Rare mesangial deposits. No TRIs. No viral particles |
|      | 4/25%/50%/50% | Severe AH | IgA (1-2+); C4d (+ in 10% of PTCs) | |
| 17   | ATN | Mild | None | Not performed |
|      | 19/0%/0%/0% | None | C4d negative | |

*SARS-CoV-2 positive by PCR at time of kidney biopsy
Abbreviations: ATN= acute tubular necrosis/acute tubular injury. TMA=thrombotic microangiopathy. FSGS=focal segmental glomerulosclerosis. GS=glomerulosclerosis. IFTA=tubular atrophy and interstitial fibrosis. GN=glomerulonephritis. TIN=tubulointerstitial nephritis. EM=electron microscopy.
AMR=antibody mediated rejection. AS= arteriosclerosis. AH=arteriolar hyalinosis. FPE=Podocyte foot process effacement. TRIs= tubuloreticular inclusions. IgAN= IgA nephropathy. ISH= in situ hybridization. Ab=antibody. Mod=moderate
Table 3. Timing and outcomes of kidney disease in patients with COVID-19

| Case # | Time between Covid-19 presentation and kidney manifestations | Time between Covid-19 presentation or PCR+ and kidney biopsy | Kidney Biopsy Diagnosis | Treatment and/or outcome at time of writing |
|--------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------|--------------------------------------------|
| 1      | Concurrent                                                 | 2 weeks*                                                    | Collapsing FSGS, ATN    | Dialysis                                  |
| 2      | No COVID-19 symptoms                                       | 4 weeks                                                    | Collapsing FSGS, ATN    | Unknown                                   |
| 3      | No COVID-19 symptoms                                       | 8 days*                                                    | Collapsing FSGS, ATN, AIN | Dialysis, with improvement in pre-dialysis Cr |
| 4      | Concurrent                                                 | 11 days                                                    | FSGS, ATN, AIN          | Unknown                                   |
| 5      | Concurrent                                                 | 7 weeks                                                    | Minimal change disease  | Prednisone; full remission after 4 weeks of treatment |
| 6      | Concurrent                                                 | 1 week                                                     | Collapsing FSGS, EM evidence of endothelial injury, ATN, TIN | Dialysis                                  |
| 7      | No COVID-19 symptoms                                       | Concurrent                                                 | Collapsing FSGS, TMA, ATN | Dialysis, no other no specific treatment. Cr returned to 1.5 |
| 8      | Concurrent                                                 | 4 days*                                                    | Arteriolar-prominent TMA, Collapsing FSGS, ATN | Dialysis – symptomatically improved with blood pressure control, but discharged to outpatient dialysis |
| 9      | No COVID-19 symptoms                                       | 25 days                                                    | Arteriolar and glomerular-prominent TMA, collapsing FSGS, ATN | Dialysis                                  |
| 10     | 3-5 days                                                   | 10-14 days*                                                | Arteriolar-prominent TMA, FSGS, mesangial immune complex deposition, ATN | Dialysis                                  |
| 11     | Concurrent                                                 | 3 days                                                     | Arteriolar and glomerular-prominent TMA | PLX, eculizumab, prednisone. Remains on dialysis |
| 12     | Unknown                                                    | 4 weeks                                                    | Post-infectious GN, advanced diabetic nephropathy, ATN | Dialysis                                  |
| 13     | Concurrent                                                 | 4 days                                                     | Advanced diabetic nephropathy, ATN | Stable and asymptomatic at the time of discharge with SCr of 1.1. Her volume status and rash had improved. Never required dialysis. |
| 14     | Concurrent                                                 | 5 days*                                                    | ATN with kappa light chain staining bias | SCr returned to 1. Eventually diagnosed with Waldenstrom’s – free light chain ratio κ/λ=15.1, κ=80.7 (normal <1.9), λ=5.35 (normal<2.35) |
| 15     | Concurrent                                                 | 6 weeks                                                    | Active AMR              | PLX+IVIG x3, IV methylprednisolone followed by rituximab |
| 16     | Concurrent                                                 | 6 weeks                                                    | Chronic active AMR, IgAN, FSGS, possible TMA | held MMF; reduced FK and initiated low dose prednisone at 10 mg q day; SCr improved to 2.7 |
| 17     | Concurrent                                                 | 7 weeks                                                    | ATN                     | SCr returned to 1.3                       |

*SARS-CoV-2 positive by PCR at time of kidney biopsy*
Abbreviations: NA=not available. PCR=polymerase chain reaction. ATN=acute tubular injury. FSGS=focal segmental glomerulosclerosis. TMA=thrombotic microangiopathy. GN=glomerulonephritis. EM=electron microscopy. IgAN=IgA nephropathy. TIN=tubulointerstitial nephritis. SCr= serum creatinine in mg/dL. IS=immunosuppression. IVIG= intravenous immunoglobulin, PLX=plasma exchange
