Acute kidney injury is a known complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection for which many different pathophysiological processes have been reported. Here, we present a case of a 45-year-old kidney transplant recipient with a breakthrough SARS-CoV-2 infection complicated by an episode of acute kidney injury 26 months after transplant. She had minimal respiratory symptoms, pancytopenia, mild hematuria, and proteinuria. A kidney biopsy revealed acute thrombotic microangiopathy (TMA) as well as an osmotic tubulopathy. The TMA was favored to be secondary to the SARS-CoV-2 infection because other etiologies for TMA, such as acute calcineurin inhibitor toxicity and acute antibody-mediated rejection, were excluded. The osmotic tubulopathy was favored to be secondary to remdesivir therapy, specifically related to the sulfobutylether-β-cyclodextrin solubilizing carrier agent used in its formulation. The patient’s kidney function improved after resolution of the SARS-CoV-2 infection. This case illustrates a unique occurrence of kidney injury secondary to SARS-CoV-2 infection and anti–COVID-19 therapy.

INTRODUCTION

Kidney injury is a prominent component of the clinical spectrum of coronavirus disease 2019 (COVID-19). Widely disparate rates of acute kidney injury (AKI) are reported among hospitalized patients with COVID-19, ranging from 0.5%-37%.1 AKI appears to involve a complex process driven by virus-mediated injury, cytokine storm, angiotensin II pathway activation, dysregulation of complement, hypercoagulation, and microangiopathy interacting with common and known risk factors for AKI. Patients with COVID-19 can also develop glomerular pathologies.2,3 Moreover, novel antiviral pharmaceuticals are in use, and their potential for kidney toxicity is yet to be fully explored. We report a case of osmotic injury associated with antiviral therapy, another reported pattern of tubular pathology related to COVID-19.

CASE REPORT

A 45-year-old woman with kidney failure secondary to collapsing glomerulopathy received a living unrelated kidney transplant, which was complicated by acute cellular rejection 1 month after transplant treated with intravenous methylprednisolone. Immunosuppression medications were tacrolimus 3 mg twice daily, mycophenolate mofetil 750 mg twice daily, and prednisone 5 mg daily. Her medical history was also significant for normocytic anemia (attributed to chronic kidney disease and immunosuppression), hypertension, obesity (weight, 225 lb; body mass index, 37.4 kg/m²), sleeve gastrectomy 25 months after transplant, obstructive sleep apnea, gestational diabetes, gestational hypertension, and preeclampsia 4 years before transplant. She had received 2 doses of Moderna COVID-19 vaccine 4 months before presentation. Tacrolimus trough 3 days before presentation was 7.1 ng/mL.

Twenty-six months after transplant, she presented with nausea, vomiting, cramping abdominal pain, and an inability to tolerate oral intake for 4 days. She was afibrile, tachycardic, and hypertensive (137/96 mm Hg) but not hypoxic. She was in no acute distress and had moist mucous membranes, clear respiratory sounds, no edema, and abdominal tenderness. The result of nasopharyngeal swab polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 was positive. She had nonoliguric AKI with a serum creatinine level of 5.86 mg/dL (baseline 2.2 mg/dL; attributed to donor size mismatch), pancytopenia, and elevated lipase (Table 1). She had 1+ protein, 3+ blood, and positive leukocyte esterase (Table 2). Urine culture grew pansensitive Escherichia coli, which was treated with ceftriaxone. Computed tomography with oral contrast showed no contrast extravasation or free intraperitoneal air and multifocal ground-glass opacities in the lung bases. An ultrasound duplex of the allograft was unremarkable. After fluid resuscitation, mycophenolate mofetil was discontinued because of COVID-19. The patient received 1 dose of the monoclonal antibody (casirivimab/imdevimab 1,200 mg in sodium chloride 0.9% 65 mL infusion) for COVID-19, and remdesivir 200 mg was given intravenously for 1 dose on the same day of presentation, followed by 100 mg daily intravenously for 4 additional doses. Because of the absence of hypoxemia, dexamethasone was not administered. Her nausea and vomiting resolved. However, her creatinine level continued to increase to 7.06 mg/dL on hospital day 7. Findings for donor-specific antibodies were negative. A kidney biopsy was performed.
The biopsy specimen (Fig 1) was composed of cortical tissue containing 49 glomeruli (13 globally sclerotic). At least 30% of the patent glomeruli and focal arterioles exhibited segmental luminal fibrin and platelet thrombi. Most uninvolved glomeruli exhibited variable ischemic changes. Proximal tubules displayed diffuse coarse to iso-metric cytoplasmic vacuolization. There was acute tubular injury and 20%-25% interstitial fibrosis/tubular atrophy. There was no significant interstitial inflammation, tubulitis, peritubular capillaritis, or glomerulitis. Arteries exhibited moderate to severe intimal sclerosis. Arterioles exhibited mild intimal hyalinosis without nodular medial hyalinosis. No oxalate crystals were present. Immunofluorescence studies demonstrated fibrinogen staining of focal glomerular thrombi, segmental granular mesangial C3 staining (2-3+), and negative C4d. Ultrastructural studies demonstrated numerous enlarged distended lysosomes filled with lucent material with proximal tubule cytoplasm. Glomerular capillary loops were corrugated, consistent with ischemia, and displayed mild endothelial cytoplasmic swelling. Occasional tubuloreticular inclusions were present. There were no double contours or viral particles. There were segmental small mesangial electron dense deposits. Peritubular capillary basement membranes were normal.

The kidney biopsy interpretation was acute thrombotic microangiopathy (TMA), acute tubular injury with osmotic tubulopathy, and low-grade glomerular C3 deposition, possibly infection-related.

Additional diagnostic testing for etiologies of thrombotic microangiopathy was obtained: ADAMTS13 (von Willebrand factor protease) activity, 118% (reference value, ≥67%); haptoglobin, 10 mg/dL (reference range, 21-210 mg/dL); C3, 91 mg/dL (reference range, 76-165 mg/L).

**Table 1. Laboratory Values**

| Laboratory      | Reference Range | Unit     | Hospital Days |
|-----------------|-----------------|----------|---------------|
| Sodium          | 135-146         | mmol/L   | 141 139 142 144 142 |
| Potassium       | 3.6-5.3         | mmol/L   | 4.4 3.5 3.4 3.7 3.7 |
| Chloride        | 96-106          | mmol/L   | 108 106 106 107 104 |
| Total CO₂       | 20-30           | mmol/L   | 18 19 22 21 23 |
| Urea            | 7-22            | mg/dL    | 50 51 54 57 58 |
| Creatinine      | 0.6-1.3         | mg/dL    | 5.86 5.97 6.72 7.06 5.91 |
| Glucose         | 65-99           | mg/dL    | 108 103 97 96 102 |
| eGFR            |                 | mL/min/1.73 m² | 9 8 8 6 9 |
| Calcium         | 8.6-10.4        | mg/dL    | 8.8 8.5 8.4 9 8.9 |
| Magnesium       | 1.4-1.9         | mg/dL    | 1.4 1.7 1.5 1.7 1.6 |
| Phosphorous      | 2.3-4.4         | mg/dL    | 3.7 4 3.9 3.9 3.7 |
| Albumin         | 3.5-4.9         | g/dL     | 3.5 3.5 3.5 3.7 |
| Total bilirubin | 0.1-1.2         | mg/dL    | 1 1 0.9 1.1 |
| AST             | 13-47           | U/L      | 23 24 33 42 |
| ALT             | 9-64            | U/L      | 14 13 23 43 |
| ALP             | 37-113          | U/L      | 86 77 66 69 |
| Ferritin        | 8-180           | ng/mL    | 1,038 971 739 |
| LDH             | 125-256         | U/L      | 512 550 437 |
| D-Dimer         | <0.6            | ng/mL    | 0.8 1.45 0.7 |
| CRP             | <0.9            |          | 6.62 1.1 0.6 |
| INR/PTT         |                 | PTT 11.5-14.4 | 1.1/13.9 |
| Hemoglobin      | 11.6-15.2       | g/dL     | 9.5 9.2 8.3 8.7 7.6 |
| Hematocrit      | 34.9%-45.2%     | %        | 29.6 28.2 27 28.1 24.5 |
| White blood cell| 4.16-9.95       | k/µL     | 2.96 3.61 3.39 4.80 5.78 |
| Platelet        | 143-398         | k/µL     | 89 82 125 150 143 |
| Abs neutrophil  | 1.80-6.90       | k/µL     | 1.47 2.48 1.39 2.29 3.28 |
| Abs lymphocyte  | 1.30-3.40       | k/µL     | 0.44 0.64 1.23 1.43 0.9 |
| Lipase          | 9-63            | U/L      | 398 |
| Amylase         | 310-124         | U/L      | 222 |
| Tacrolimus trough |            | ng/mL    | 9.8 11.3 12.5 2.7 |
| CMV             | Not detected    |          | <137 |
| TSH             | 1.3             |          | |

Abbreviations: Abs, Absolute; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CMV, cytomegalovirus; CO₂, carbon dioxide; CRP, C-Reactive protein; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, prothrombin time; TSH, thyroid stimulating hormone.
dL); C4, 37 mg/dL (reference range, 14-46 mg/dL), and complement activity alternative pathway, 136% (reference value, >59%). Peripheral smear did not show schistocytes.

During her hospitalization, tacrolimus dose was adjusted because of the supratherapeutic tacrolimus level attributed to CYP3A4 inhibition by remdesivir. The

Table 2. Urine analysis

|                      | Reference Range | Unit   | 2 mo Prior Admission | Hospital Day 0 | 3 mo After Discharge |
|----------------------|-----------------|--------|----------------------|----------------|----------------------|
| Urine color          | Yellow          | Yellow | Yellow               | Hospital Day 0 | 3 mo After Discharge |
| Specific gravity     | 1.005-1.030     |        | 1.021                | 1.011          | 1.015                |
| pH, urine            | 5.0-8.0         |        | 5.5                  | 5.5            | 6.0                  |
| Blood                | Negative        | 2+     | Negative             | Negative       | Negative             |
| Bilirubin            | Negative        |        | Negative             | Negative       | Negative             |
| Ketones              | Negative        |        | Negative             | 1+             | Negative             |
| Glucose              | Negative        |        | Negative             | Negative       | Negative             |
| Protein              | Negative        |        | 1+                   | 1+             | Negative             |
| Leukocyte esterase   | Negative        |        | Negative             | Negative       | Negative             |
| Nitrite              | Negative        |        | Negative             | Negative       | Negative             |
| RBC per μL           | 0-11 cells/μL   | 48     | >1,000               | 5              |
| WBC per μL           | 0-22 cells/μL   | 3      | 56                   | 6              |
| RBC per HPF          | 0-2 cells/HPF   | 10     | >210                 | 1              |
| WBC per HPF          | 0-4 cells/HPF   | 1      | 11                   | 1              |
| Bacteria             | Absent          |        | Present              |                |
| Squamous epithelial cells | 0-17 cells/μL | 3      | 3                    |
| Sodium, random urine | mg/dL           | 82     |                      |
| Creatinine, random urine | mg/dL     | 93.2   |                      |
| Urea nitrogen, random urine |             | 430    |                      |
| Urine albumin to creatinine ratio | <30 μg/mg | 63     |                      |
| Urine protein to creatinine ratio | 0.0-0.4 | 0.3    |                      |

Abbreviations: HPF, High-power field; RBC, red blood cell; WBC, white blood cell.

Figure 1. Acute glomerular predominant thrombotic microangiopathy and osmotic tubulopathy. Glomeruli with luminal thrombi (A) periodic acid–Schiff stain (original magnification, ×400), (B) fibrinogen staining of fibrin thrombus (original magnification, ×400). Arrows point to thrombi. (C) Prominent tubular cytoplasmic vacuolization (toluidine blue stain; original magnification, ×400). Arrow points to tubular cytoplasmic vacuolization. (D and E) Electron micrograph of proximal tubule with cytoplasmic vacuoles. Arrow points to tubular cytoplasmic vacuolization. (F) Tubuloreticular inclusion (arrow) in glomerular endothelial cells.
patient’s kidney function started to improve on hospital day 9. The serum creatinine level was 5.91 mg/dL before discharge and 3.34 mg/dL 1 week after discharge. The most recent serum creatinine level was 3.42 mg/dL, which was 2 months after her admission.

**DISCUSSION**

TMA associated with COVID-19 has been previously reported. Evidence suggests that severe acute respiratory syndrome coronavirus 2 infection leads to cytokine storm–mediated kidney injury through the activation of the alternative pathway of the complement rather than direct viral infection of the kidney. The presence of low-grade C3 deposition within the glomerulus seen in this case may further implicate the alternative complement activation or, possibly, a concurrent low-grade infection–related glomerulopathy. Interestingly, COVID-19–associated kidney diseases, including TMA, often occur even with mild pulmonary and systemic COVID-19 disease.

Etiologies for TMA are diverse, and there are no specific findings on kidney biopsy specimens that can discriminate among them. Alternative differential diagnoses for TMA in this case include tacrolimus-induced TMA and active antibody-mediated rejection. The patient’s tacrolimus trough was in the 7-9 ng/mL range for at least 1 year before presentation, and her serum creatinine level was stable until the severe acute respiratory syndrome coronavirus 2 infection. The patient also had multiple prior allograft biopsies without evidence of acute or chronic tacrolimus effects. Tacrolimus trough 3 days before presentation was 7.1 ng/mL, and the thrombocytopenia was improving during her hospital stay despite development of slightly supratherapeutic tacrolimus trough levels. Thus, tacrolimus-induced TMA is a less likely etiology for the patient’s AKI or pathologic findings. Because this patient had no other evidence for antibody-mediated rejection (eg, no microvascular inflammation, C4d negative, or serum donor-specific antibodies), the possibility of antibody-mediated rejection associated TMA was thought to be unlikely.

Other less likely etiologies of TMA, such ADAMTS13 deficiency, other infections, antiphospholipid antibodies, and drug-associated TMA, were also ruled out. An underlying complement-mediated TMA with COVID-19 as a trigger is also a possibility; however, a more extensive complement system evaluation (eg, genetic studies) was not performed because the patient’s kidney function improved after COVID-19 resolution.

Osmotic tubulopathy describes a morphologic pattern, with vacuolization and swelling seen when proximal tubules are overwhelmed by a load of indigestible carbohydrates. Injury is favored to be because of pinocytosis with uptake into lysosomes. Osmotic tubulopathy is generally associated with mannitol, low-molecular-weight dextrans, intravenous radiologic contrast media, hydroxyethyl starch, excess glucose, methanol, and gelatin. Our patient did not receive any of these agents. The patient’s blood glucose was normal or near normal, and urine glucose was negative at the time of admission. Additionally, no reports suggest that casirivimab/imdevimab causes AKI, tacrolimus interaction, or pathologic changes on kidney biopsy, and it has been tolerated by kidney transplant patients.

Remdesivir is a nucleotide analog that inhibits viral ribonucleic acid–dependent ribonucleic acid polymerase. Remdesivir formulation contains sulfobutylether-β-cyclodextrin as a solubilizing carrier agent, and we postulate that this contributed to osmotic tubulopathy in our patient. At least 1 prior case of remdesivir osmotic tubulopathy has been reported. Sulfobutylether-β-cyclodextrin is a large, cyclic oligosaccharide that is predominantly excreted through glomerular filtration. A preclinical study suggested that reversible cytosolic vacuolation in kidney tubular epithelial cells was observed as low as 160 mg/kg in rats. Each 100 mg of lyophilized powder and solution of remdesivir contain 3 and 6 g of sulfobutylether-β-cyclodextrin, respectively, and our patient received a total of 600 mg of the lyophilized form of remdesivir. The use of remdesivir with decreased kidney function is relatively safe. Although 11.7% of kidney transplant recipients reported elevated levels of serum creatinine after remdesivir therapy, none reported discontinuation of therapy.

The primary differential diagnosis of the tubular vacuolar change seen in this case is calcineurin inhibitor toxicity, which is characterized by isometric vacuolization and may be indistinguishable from osmotic tubulopathy. The tubular cytoplasmic vacuolization observed in our case was diffuse and variably coarse, which is not typical for acute calcineurin inhibitor toxicity, which usually shows focal fine isometric vacuolization. Other convincing morphologic features of calcineurin inhibitor nephrotoxicity (eg, myocyte cytoplasmic vacuolization and dropout, focal nodular hyalinosis) were not present. Thus, we believe that the osmotic tubulopathy was mostly likely because of remdesivir therapy. Interestingly, remdesivir is a weak CYP3A4 inhibitor that may lead to increased tacrolimus levels and could explain the slightly supratherapeutic tacrolimus trough levels that developed during the patient’s admission.

In summary, the patient’s clinical course and kidney biopsy findings support that this patient’s AKI was most likely secondary to a COVID-19–associated TMA, possibly exacerbated by an osmotic tubulopathy secondary to remdesivir therapy. This case illustrates that severe COVID-19–associated kidney disease can occur even with an otherwise mild severe acute respiratory syndrome coronavirus 2 infection and that novel treatments such as remdesivir may result in renal biopsy histologic perturbations.
ARTICLE INFORMATION

Authors’ Full Names and Academic Degrees: Peter Fahim, MD, Anthony Nicolaysen, MD, Julie M. Yabu, MD, and Jonathan E. Zuckerman, MD, PhD

Authors’ Affiliations: Division of Nephrology, Department of Medicine (PF, AN, JMY), and Department of Pathology and Laboratory Medicine (JEZ), University of California, Los Angeles, CA.

Address for Correspondence: Jonathan E. Zuckerman, MD, PhD, UCLA Center for Health Sciences, 10833 Le Conte Ave, Los Angeles CA 90095 (email: JZuckerman@mednet.ucla.edu) or Julie M. Yabu, MD, Division of Nephrology, Department of Medicine, University of California, 700 Tiverton Ave, 7-155 Factor Building, Mail Code 168917, Los Angeles, CA 90095 (email: jyabu@mednet.ucla.edu)

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Patient Protections: The authors declare that they have obtained consent from the patient reported in this article for publication of the information about him/her that appears within this Case Report and any associated supplementary material.

Peer Review: Received January 25, 2022 as a submission to the expedited consideration track with 3 external peer reviews. Direct editorial input from the Editor-in-Chief. Accepted in revised form March 27, 2022.

REFERENCES

1. Husain-Syed F, Birk HW, Ronco C. Coronavirus disease 2019 and acute kidney injury: what have we learned? Kidney Int Rep. 2021;6(4):872-874. doi:10.1016/j.ekir.2021.02.035
2. Akilesh S, Nast CC, Yamashita M, et al. Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. Am J Kidney Dis. 2021;77(1):82-93.e1. doi:10.1053/j.ajkd.2020.10.001
3. May RM, Cassol C, Hannoudi A, et al. A multi-center retrospective cohort study defines the spectrum of kidney pathology in coronavirus 2019 disease (COVID-19). Kidney Int. 2021;100(6):1303-1315. doi:10.1016/j.kint.2021.07.015
4. Ahmadian E, Hosseiniyan Khatibi SM, Razi Soofiyani S, et al. Covid-19 and kidney injury: pathophysiology and molecular mechanisms. Rev Med Virol. 2021;31(3):e2176. doi:10.1002/rmv.2176
5. Phadke G, Kaushal A, Tolan DR, et al. Osmotic nephrosis and acute kidney injury associated with SGLT2 inhibitor use: a case report. Am J Kidney Dis. 2020;76(1):144-147. doi:10.1053/j.ajkd.2020.01.015
6. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. Am J Kidney Dis. 2008;51(3):491-503. doi:10.1053/j.ajkd.2007.10.044
7. Dhand A, Lobo SA, Wolfe K, et al. Casirivimab-imbdevimab for treatment of COVID-19 in solid organ transplant recipients: an early experience. Transplantation. 2021;105(7):e68-e69. doi:10.1097/TP.0000000000003737
8. Liu EC, Lee JH, Loo A, et al. Casirivimab-imbdevimab (REGN-COV2) for mild to moderate SARS-CoV-2 infection in kidney transplant recipients. Kidney Int Rep. 2021;6(11):2900-2902. doi:10.1016/j.ekir.2021.08.032
9. Davis MR, Pham CU, Cies JJ. Remdesivir and GS-441524 plasma concentrations in patients with end-stage renal disease on haemodialysis. J Antimicrob Chemother. 2021;76(3):822-825. doi:10.1093/jac/dkaa472
10. Wongboonsin J, Shah SI, Marty FM, Mount DB, Rennke HG, Murakami N. Osmotic tubulopathy in a patient with COVID-19 treated with remdesivir. Kidney Int Rep. 2021;6(7):1987-1991. doi:10.1016/j.ekir.2021.04.032
11. Kiser TH, Fish DN, Aquilante CL, et al. Evaluation of sulfobutylether-β-cyclodextrin (SBECD) accumulation and voriconazole pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. Crit Care. 2015;19(1):32. doi:10.1186/s13054-015-0753-8
12. Buxeda A, Arias-Cabrales C, Pérez-Sáez MJ, et al. Use and safety of remdesivir in kidney transplant recipients with COVID-19. Kidney Int Rep. 2021;6(9):2305-2315. doi:10.1016/j.ekir.2021.06.023
13. Lusco MA, Fogo AB, Najatian B, Alpers CE. AJKD atlas of renal pathology: calcineurin inhibitor nephrotoxicity. Am J Kidney Dis. 2017;69(5):e21-e22. doi:10.1053/j.ajkd.2017.02.003
14. Salerno DM, Kovac D, Corbo H, et al. SARS-CoV-2 infection increases tacrolimus concentrations in solid-organ transplant recipients. Clin Transplant. 2021;35(3):e14193. doi:10.1111/ctr.14193