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COVID-19 Manifesting as Renal Allograft Dysfunction, Acute Pancreatitis, and Thrombotic Microangiopathy: A Case Report

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ABSTRACT
Coronavirus disease 2019 (COVID-19) is associated with high morbidity and mortality worldwide in both the general population and kidney transplant recipients. Acute kidney injury is a known complication of COVID-19 and appears to most commonly manifest as acute tubular injury on renal biopsy. Coagulopathy associated with COVID-19 is a known but poorly understood complication that has been reported to cause thrombotic microangiopathy on rare occasions in native kidneys of patients with COVID-19. Here, we report the first case of biopsy-proven thrombotic microangiopathy in a kidney transplant recipient with COVID-19 who developed acute pancreatitis and clinical features of microangiopathic hemolytic anemia. The patient recovered with supportive care alone.

THE spread of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic with more than 86 million confirmed cases and more than 1.8 million deaths around the world as of January 6, 2021 [1]. Observational studies of kidney transplant recipients diagnosed with COVID-19 demonstrated higher mortality rates compared to the general population and frequent allograft dysfunction [2–5]. In the general population, acute kidney injury associated with COVID-19 is a common complication, the mechanism of which still remains unclear. Though acute tubular injury appears to be the most common histopathologic finding, cases of thrombotic microangiopathy (TMA) have been described in native kidneys [6,7]. Here we report the first case of biopsy-proven TMA in a renal transplant patient with SARS-CoV-2 infection, manifesting as gastrointestinal symptoms with acute pancreatitis. Subsequently, the patient’s TMA resolved and her allograft function recovered with supportive care alone.

CASE DESCRIPTION
A 49-year-old woman with chronic kidney disease secondary to focal segmental glomerulosclerosis received a preemptive renal transplant from a donation after cardiac death donor with a Kidney Donor Profile Index of 18%. The recipient was highly sensitized with calculated panel-reactive antibodies of 63% at time of transplantation and received thymoglobulin induction therapy. Maintenance immunosuppression consisted of tacrolimus, mycophenolate, and prednisone. Following transplant, the patient experienced slow graft function with suboptimal creatinine at ~2 mg/dL, which prompted a biopsy at 6 weeks posttransplant. This biopsy showed acute tubular injury with mild to moderate interstitial fibrosis and tubular atrophy, without evidence of acute rejection. No adjustments were made to her immunosuppression, and her serum creatinine remained suboptimal, fluctuating between 1.6 and 2.1 mg/dL. She subsequently underwent a 3-month surveillance biopsy, the findings of which were similar to those of the previous biopsy.

One week later, the patient was admitted to a local hospital with diarrhea, generalized weakness, and menorrhagia. She was found to have acute kidney injury (AKI) with serum creatinine of 2.81 mg/dL and anemia with hemoglobin of 9.5 g/dL, which decreased to 7.7 g/dL after 48 hours (Table 1). Cytomegalovirus viral load, parvovirus B19 viral load, and peripheral blood cultures were negative. Tacrolimus trough was within target therapeutic range. Her AKI was attributed to pre-renal etiology and renal function improved with intravenous fluids. She was discharged home after receiving a transfusion of packed red cells. SARS-CoV-2 polymerase chain
Table 1. Laboratory Values During Clinical Course

| Event                          | Day 1 | Day 3 | Day 12 | Day 15 | Day 18 | Day 20 | Day 21 | Day 22 |
|-------------------------------|-------|-------|--------|--------|--------|--------|--------|--------|
| Hemoglobin (12-16 g/dL)       | 9.5   | 7.7   | 8.9    | 7.8    | 7.7    | 5.9    | 9.2    | 9.2    |
| Platelets (130-400 K/uL)      | 228   | 193   | 128    | 116    | 88     | 52     | 90     | 104    | 103    |
| Schistocytes                  | Slight| Slight| Slight | Slight | Slight | Slight | Slight | Marked |
| Creatinine (mg/dL)            | 2.81  | 2.34  | 4.04   | 3.51   | 3.99   | 4.94   | 5.64   | 5.85   | 6.13   |
| Lipase (13-51 U/L)            | 75    | 2864  | 533    | 147    |        |        |        |        |
| Tacrolimus level (ng/mL)      | 14.5  | 10.8  |        |        |        |        |        |        |
| D-dimer (<0.49 mg/L FEU)      |       |        |        |        |        |        |        |        |
| Haptoglobin (30-220 mg/dL)    |       |        |        |        |        |        |        |        |
| Lactate dehydrogenase (0-200 U/L) |       |        |        |        |        |        |        |        |

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DISCUSSION

As the prevalence of COVID-19 has increased, we are now beginning to realize that infected individuals can experience a wide range of extrapulmonary symptoms, including renal, gastrointestinal, and hematologic manifestations. Renal
dysfunction is a well-recognized complication of COVID-19, affecting more than 30% of hospitalized patients [8]. Our knowledge of the pathology in both native and transplant kidneys associated with this infection is evolving as limited observational studies and case reports emerge amidst the pandemic. Based on autopsy and biopsy material, acute tubular injury appears to be the most common histopathologic finding in COVID-19 patients with AKI [9–11]. Collapsing glomerulopathy has also been reported in some infected patients, particularly those with APOL1 kidney disease risk variants [12,13]. The exact mechanism of kidney injury is still unclear but is likely multifactorial. Debate remains regarding whether there is evidence for direct viral infection of the kidney by SARS-CoV-2 [9,14,15].

Coagulopathy is a well-recognized complication of COVID-19 that primarily manifests as venous thromboembolism but also arterial thrombosis. However, microvascular thrombosis in the kidney can occur in the setting of COVID-19 and is likely a contributor to renal injury in some patients. Recently, a case of biopsy-proven TMA with renal cortical necrosis and clinical manifestation of microangiopathic hemolytic anemia in the native kidney was reported [6]. Here, we describe the first case of renal allograft biopsy-proven TMA in a transplant patient with COVID-19. Correlating clinical evidence of microangiopathic hemolytic anemia was observed, characterized by low haptoglobin, elevated lactate dehydrogenase, and schistocytes on peripheral smear, as well as thrombocytopenia.

A wide range of etiologies can cause TMA, including ADAMTS13 deficiency, Shiga toxin–mediated injury, alternative complement pathway abnormalities, and medication-induced injury, among others. In the transplant setting, common etiologies to consider include calcineurin inhibitor (CNI) nephrotoxicity (often occurring in a dose-dependent manner) and acute antibody-mediated rejection. In our patient, although we could not absolutely exclude CNI as the etiology for TMA, it was unlikely to be the causative factor given the lack of excessively elevated tacrolimus levels as well as the complete resolution of her TMA-related hematological abnormalities and allograft dysfunction without CNI cessation. The biopsy findings did not disclose any evidence to suggest rejection, and donor-specific antibodies were negative, thus excluding acute antibody-mediated rejection as a cause. Given these findings, and the fact that TMA developed and resolved in conjunction with SARS-CoV-2 infection, COVID-19 was the most likely cause of TMA in this case.

Fig 2. Histopathologic and ultrastructural findings on renal biopsy. (A) Hematoxylin and eosin–stained and (B) Jones methenamine silver–stained glomeruli demonstrating luminal closure with intimal edema, fibrin thrombi, and fragmented red blood cells in the hilar arterioles (400× magnification). (C) Small artery with fibrin thrombus and fragmented red blood cells (hematoxylin and eosin stain; 400× magnification). (D) Electron micrograph showing wrinkling of the glomerular basement membrane with endothelial cell swelling (4800× magnification).
Our patient had an atypical COVID-19 presentation and clinical course given that she never had respiratory symptoms or radiographic lung abnormalities. Instead, she experienced mainly gastrointestinal symptoms, which included diarrhea and acute pancreatitis. She had no history of acute pancreatitis and no predisposing factors such as hypertriglyceridemia or alcohol use. Acute pancreatitis can rarely develop as a complication of TMA. Given that her gastrointestinal symptoms preceded laboratory findings of microangiopathic hemolytic anemia and because acute pancreatitis is a known but rare presentation for COVID-19 [16,17], her acute pancreatitis was most likely a result of SARS-CoV-2 infection rather than secondary to TMA. Of note, acute pancreatitis has also been reported as a rare cause of TMA [18,19] and thus the possibility that our patient’s TMA was a result of COVID-19-associated acute pancreatitis cannot be excluded.

Transplant patients with COVID-19 can present many unique challenges. Our case illustrates that extrapulmonary manifestations of COVID-19 can play an important part during the course of illness. When diagnosing and treating kidney transplant recipients with AKI in the setting of COVID-19, clinicians should add TMA to the differential for allograft injury.

DATA AVAILABILITY
Data will be made available on request.

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