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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

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**Table 1. Laboratory Values During Clinical Course**

| Event | Day 1 Initial Presentation | Day 3 Initial Discharge | Day 12 Readmission | Day 13 | Day 15 | Day 18 | Day 20 | Day 21 | Day 22 Transferred Hospitals |
|---|---|---|---|---|---|---|---|---|---|
| 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 | 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 μg/mL FEU) | | | | | >4 | | | | |
| Haptoglobin (30-220 mg/dL) | | | | | | | 12 | | |
| Lactate dehydrogenase (0-200 U/L) | | | | | | | 1017 | | |

reaction screening results returned positive 2 days later, although the patient had no respiratory symptoms.

The patient returned to the local hospital 9 days after discharge with worsening diarrhea, abdominal pain, and limited oral intake and was found to have progressive renal failure with serum creatinine at 4.04 mg/dL, recurrent anemia with hemoglobin of 8.9 mg/dL, and new thrombocytopenia with platelet count of 128,000/μL (Table 1 and Fig 1). Except for persistently positive SARS-CoV-2 polymerase chain reaction, workup for diarrhea was unrevealing, including negative stool cultures for bacteria, ova, and parasites. Computed tomography scan of the abdomen demonstrated peripancreatic edema and fluid suspicious for acute pancreatitis in conjunction with an elevated lipase to 2864 U/L. Serum triglyceride level was normal at 158 mg/dL, and the patient denied alcohol use. Over the subsequent days, anemia and thrombocytopenia worsened with nadir at 5.9 mg/dL and 52,000/μL, respectively. D-dimer was elevated at >4 μg/mL fibrinogen equivalent units, but nuclear medicine scan did not support pulmonary embolus. A pelvic ultrasound for evaluation of menorrhagia demonstrated only a leiomyomatous uterus. Renal ultrasound showed patent vasculature and normal perfusion to the transplanted kidney without signs of renal artery stenosis or hydronephrosis. Renal function continued to deteriorate, and creatinine reached a peak of 6.13 mg/dL. The patient was then found to have low haptoglobin of 12 mg/dL and elevated lactate dehydrogenase of 1017 U/L, and schistocytes were present on peripheral blood smear, all features concerning for hemolytic anemia.

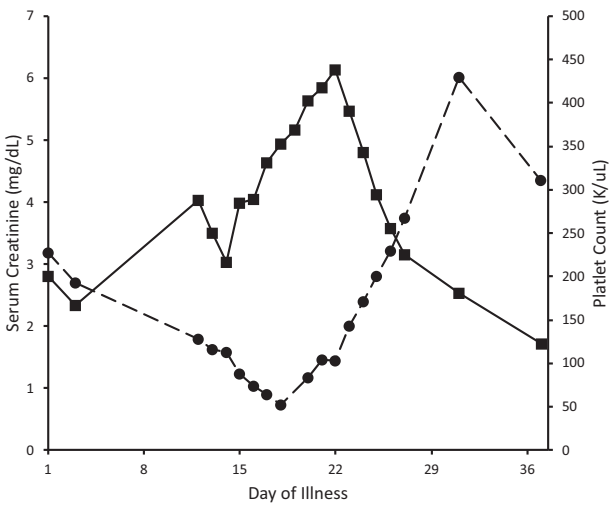


**Fig 1.** Serum creatinine (solid line) and platelet count (dashed line) throughout the course of illness and follow-up period.

The patient was ultimately transferred to our institution and a transplant kidney biopsy was performed at 4 months posttransplant. Light microscopy contained more than 20 glomeruli, of which 1 was globally sclerotic. At least 5 glomeruli showed significant narrowing or obliteration of the hilar arteriolar lumina, with presence of intimal edema, fragmented red blood cells, and/or fibrin thrombi (Figs 2A and 2B). Many of these glomeruli demonstrated associated wrinkling of the glomerular capillary walls. Focally, small arteries exhibited fibrin thrombi with associated fragmented red blood cells (Fig 2C). Acute tubular injury was present, as well as mild interstitial fibrosis and tubular atrophy. No significant microvascular inflammation (ie, glomerulitis or peritubular capillaritis) or tubulitis was present, and only minimal interstitial inflammation was identified. Immunofluorescence was negative, including C4d. Electron microscopy showed segmental wrinkling of the glomerular basement membrane, as well as patchy swelling of the endothelial cells (Fig 2D). No immune deposits were present. Overall, the main diagnostic finding was that of TMA, supported by the changes seen in the small arteries and arterioles.

Review of tacrolimus levels demonstrated that they were at therapeutic goal. However, because the presence of TMA on the biopsy, the tacrolimus target trough was reduced to 4 to 6 ng/mL. Donor-specific antibodies were negative. The patient's symptoms and laboratory markers improved spontaneously toward the end of the hospitalization with normalization of platelet count and haptoglobin, as well as a decrease in lactate dehydrogenase and lipase levels. Her creatinine steadily improved to 3.15 mg/dL (from peak of 6.1 mg/dL) at time of discharge. Creatinine further normalized to 1.71 mg/dL 10 days after discharge (Fig 1).

Of note, although the patient was positive for SARS-CoV-2, she did not demonstrate any respiratory symptoms during the entire course of illness. Chest radiographs only showed mild atelectasis, without evidence of infection, and she never required supplemental oxygen. Her symptoms were largely gastrointestinal in nature, including acute pancreatitis. She had no prior history of acute pancreatitis and had no risk factors or comorbidities that would predispose her to acute pancreatitis.

## 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

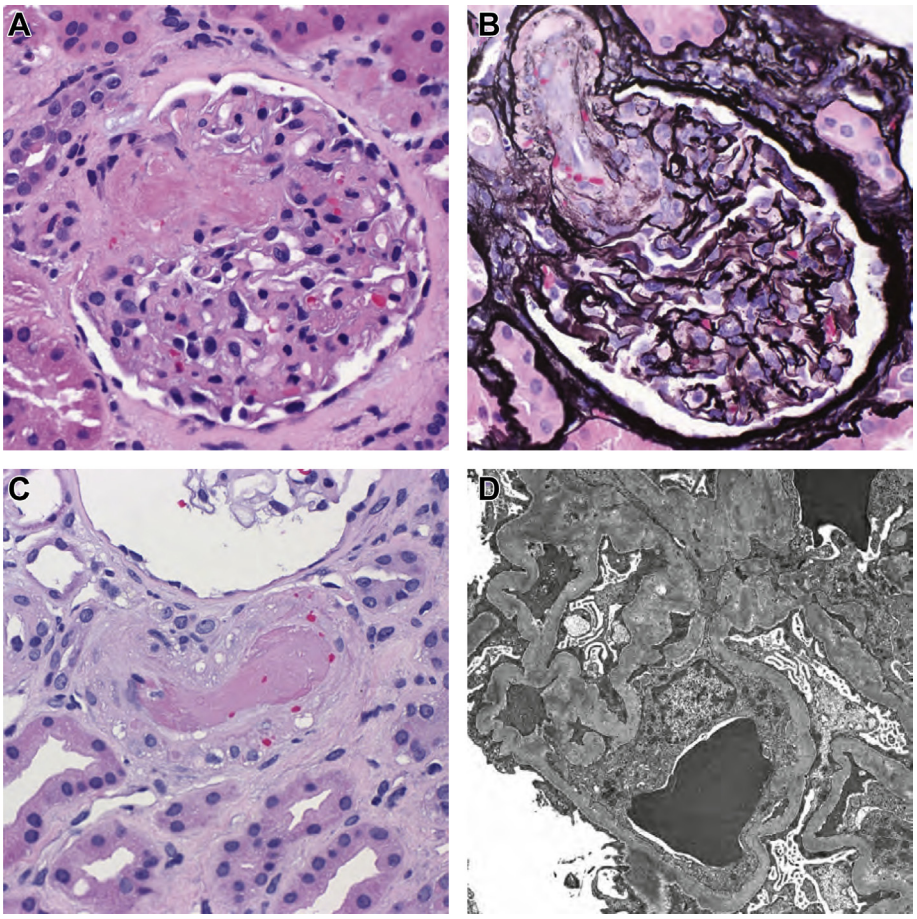


**Fig 2.** Histopathologic and ultrastructural findings on renal biopsy. **(A)** Hematoxylin and eosin–stained and **(B)** Jones methenamine silver–stained glomeruli demonstrating luminal closure with intimal edema, fibrin thrombi, and fragmented red blood cells in the hilar arterioles (400× magnification). **(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).



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.

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.

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