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Chronic Active Antibody-Mediated Rejection Following COVID-19 Infection in a Kidney Transplant Recipient: A Case Report

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ABSTRACT

Kidney transplant recipients who develop coronavirus disease 2019 (COVID-19) are at increased risk of life-threatening illness, which often requires reducing immunosuppression despite the potential risk of causing an allograft rejection. Herein, we describe the clinical presentation and course of a kidney transplant recipient who acquired COVID-19 and was hospitalized with severe symptoms and hypoxemia. Upon admission, the patient was found to have elevated de novo donor-specific antibodies (DSA) yielding a positive cytotoxicity crossmatch and concurrent elevated plasma donor-derived cell-free DNA (dd-cfDNA) level, indicating a possible ongoing rejection despite improvement in his serum creatinine. Because of persistent positive COVID-19 tests and stable serum creatinine, a kidney allograft biopsy was initially deferred and his dd-cfDNA and DSA were monitored closely postdischarge. Three months later, because of persistent elevated dd-cfDNA and positive DSA, a kidney allograft biopsy was performed, which showed chronic active antibody-mediated rejection. Accordingly, the patient was treated with intravenous immunoglobulin and his maintenance immunosuppressive regimen was increased.

TREATMENT of kidney transplant recipients who acquire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is challenging to health care professionals [1,2]. Their chronic immunosuppressed status and coexisting medical conditions put them at an increased risk of complications and higher mortality [3]. Reduction of immunosuppression, particularly discontinuation of the antimetabolite, in the setting of coronavirus disease 2019 (COVID-19) is a common practice [4,5]. Accordingly, the risk of allograft rejection, especially among high-risk transplant recipients, might be increased in the presence of ongoing infection with reduced immunosuppression and the not infrequent subtherapeutic calcineurin inhibitor levels in the presence of gastrointestinal upset and vomiting seen in COVID-19. Although histology obtained via needle biopsy remains the gold standard for the diagnosis of rejection, this technique is infrequently used for surveillance because of the cost, potential complications, and patient's inconvenience [6]. In transplant recipients with COVID-19, a kidney allograft biopsy poses more challenges because the patients might be acutely ill, under meticulous isolation precautions, and possibly in a prone position. In addition, the risk would likely outweigh the benefits, especially in the presence of severe infection that precludes the use of "heavy" immunosuppression even in the presence of an ongoing rejection. Plasma donor-derived cell-free DNA (dd-cfDNA) detected in the blood of kidney transplant recipients has been proposed as a noninvasive marker for diagnosis of kidney allograft rejection. In this article, we present a kidney transplant recipient with COVID-19 infection who had serial elevated dd-cfDNA tests following COVID-19 illness and eventually a confirmed diagnosis of biopsy-proven chronic active antibody-mediated rejection (ABMR).

CASE PRESENTATION

A 54-year-old African American man with a medical history of end-stage kidney disease secondary to diabetes mellitus and hypertensive nephrosclerosis underwent a 3 antigen-mismatched

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(HLA-1A, -1B, -1DR) deceased-donor kidney transplant in October 2018 and was maintained on triple immunosuppression with tacrolimus (target trough 4-7 ng/mL), mycophenolate 1000 mg twice daily, and prednisone 5 mg daily. His posttransplant baseline serum creatinine (SCr) was 1.4 to 1.6 mg/dL, and he had no baseline proteinuria.

Eighteen months following his kidney transplant, the patient developed a fever of 100.7°F and watery diarrhea with 5 to 6 bowel movements daily for 3 days associated with nausea and a few episodes of vomiting. He also noticed loss of taste and smell. Accordingly, he was tested for COVID-19 via nasopharyngeal swab, which was positive for SARS-CoV-2. He was initially seen virtually through a telemedicine visit, at which time his vital signs were blood pressure (BP) of 134/73 mm Hg and pulse of 86 bpm. He reported no shortness of breath, chest pain, or cough. The patient was advised to increase oral fluid intake, monitor his symptoms, and self-quarantine at home with frequent monitoring of his vital signs. His mycophenolate dose was reduced to 500 mg twice daily.

Two days following the tele-visit, he reported increased lethargy and reduced oral intake. He missed his medications, including his immunosuppressive medications, for 2 days and continued to have watery diarrhea. He was referred to the emergency department for further evaluation and possible admission. In the emergency department, his BP was 144/71 mm Hg, pulse 86 bpm, temperature 99.9°F, respiratory rate 20 breaths per minute, and oxygen saturation 93% on room air. Physical exam was remarkable for dry mucous membranes, and chest exam revealed bilateral coarse crepitations over lower lung zones. A chest x-ray showed bilateral peripheral patchy opacities, compatible with COVID-19 pneumonia. Urinalysis was remarkable for 2+ protein, and 5 red blood cells per high power field. His initial labs showed SCr of 2.6 mg/dL; blood urea nitrogen, 61 mg/dL; white blood cell count, 8.32 K/cu mm; absolute lymphocyte count, 0.69 K/cu mm; hemoglobin, 12.6 g/dL; and platelets, 231,000 K/cu mm. Serum ferritin was 4028 ng/mL; erythrocyte sedimentation rate, 89 mm/h; C-reactive protein, 13.8 mg/dL; and interleukin-6, 64.6 pg/mL. He was started on intravenous fluids, mycophenolate was discontinued, and he was placed on oxygen at 3 L/min via nasal cannula. An ultrasound of the renal allograft showed mild hydronephrosis.

The following day (day 2 of admission), his oxygen requirements worsened, requiring 70% FiO_2 via high-flow nasal cannula. He was kept in a prone position and was started on intravenous cefepime and oral doxycycline to cover for a possible superimposed bacterial infection and he was started on isavuconazole and micafungin to empirically cover for fungal infections. Given his high inflammatory markers and increased oxygen demands, he received intravenous tocilizumab at 4 mg/kg and was started on valacyclovir for viral prophylaxis. His SCr increased to 3.4 mg/dL despite fluids. A bladder scan showed 448 mL of urine and accordingly a Foley's catheter was inserted. Tacrolimus level was elevated at 16.6 ng/mL and the dose was adjusted. On hospital day 4, his oxygen requirements started to improve, SCr began to trend downward to 2.8 mg/dL, and C-reactive protein trended downward to 2.9 mg/dL. He continued to have clinical improvement and was weaned off oxygen and his SCr continued to improve.

Because of the history of low-level donor-specific antibodies (DSAs) to HLA-DR7 and -DR53 (well below flow cytometric crossmatch level), a test was done on day 12 of hospital admission, which showed continued presence of DSAs to HLA-DR7 and -DR53 and, of concern, new DSAs to HLA-DQA2 and -DQB2 were present at a level compatible with a positive cytotoxicity crossmatch. At that time, SCr was 1.6 mg/dL, which was close to baseline, and the urine protein-to-creatinine (UPC) ratio was 0.7 g/g. On hospital day 14, another sample showed continued presence of DSAs to HLA-DR7, -DR53, -DQA2, and -DQB2 and DSAs to HLA-DQB9 and -DP20 were present. Collectively, DSAs were at a levels sufficient to yield a positive cytotoxicity crossmatch. Additionally, plasma dd-cfDNA level was tested and was elevated at 4.3%. Because of the improvement in SCr, we decided to avoid renal biopsy and continue close monitoring. On hospital day 16, the patient was discharged home because he was completely off oxygen support for multiple days and was symptom free. SCr on discharge was 1.9 mg/dL and tacrolimus levels were at goal (4-7 ng/mL).

Serial follow-up dd-cfDNA levels, along with DSA, SCr, and tacrolimus levels and COVID-19 tests, are shown in Table 1. dd-cfDNA continued to be elevated; however, because of the stable SCr level and persistent positive COVID-19 tests, a renal biopsy was deferred. On day 73 following discharge, the patient complained of a 30 lb weight gain, with worsening bilateral lower limb and scrotal edema associated with elevated BP and proteinuria of 0.56 g/g on UPC. He was admitted to the hospital for intravenous diuresis. Following diuresis, his SCr rose to 2 mg/dL and a recent dd-cfDNA was elevated at 3.5%. Accordingly, he underwent a renal allograft biopsy, which showed features of chronic active ABMR (g3, i1, t0, v0, ptc3, ti1, cg3, ci0-1, ct0-1, cvX, mm3, ah0, C4d0; Fig 1). He received a total of 1 gm/kg of intravenous immunoglobulin and was restarted on mycophenolate 250 mg twice daily because his absolute lymphocyte count at that time was 1.1 K/cu mm. His edema improved with diuresis and he was discharged on oral diuretics. His most recent SCr was 1.5 g/dL and UPC was 0.8 g/g (obtained 23 months posttransplant and 5 months following initial COVID-19 presentation).

DISCUSSION

When the COVID-19 pandemic unfolded, special concerns were raised in particular with regard to solid organ transplant recipients [7]. Multiple studies showed higher disease severity and mortality among these patients [1,8]. Thus, a careful approach should be sought to achieve a balance between the risk of a severe and possibly life-threatening illness and the potential risk of "rejecting" the allograft as a result of reducing or withholding immunosuppression. In this article, we highlighted the latter.

In our patient, the presence of preexisting low-level de novo DSAs (which were absent at the time of transplant) placed him at an increased risk for developing ABMR. The severity of COVID-19 infection necessitating reduction of immunosuppression potentially triggered further new HLA DSAs, which were not present prior to his presentation, in addition to his previous HLA DSA. His initial acute kidney injury was clinically explained by reduced oral intake, diarrhea, elevated tacrolimus level, and urinary retention; rejection was less likely. However, the patient did receive tociluzumab as a part of COVID-19 directed therapy, which was followed by an improvement in SCr. Tociluzumab is proposed as a treatment modality for acute ABMR [9] and for chronic active ABMR [10,11]. When used for rejection, the dose is higher and is given monthly [10]. The improvement in SCr in our patient to a value close to baseline

Table 1. Serial Serum Creatinine, Tacrolimus Level, dd-cfDNA, and COVID-19 Tests During Hospitalization and Postdischarge*

	Hospital Day 1	Hospital Day 14	Hospital Day 16 (Discharge Day)	Day 14 Postdischarge	Day 35 Postdischarge	Day 56 Postdischarge	Day 70 Postdischarge	Day 73 Postdischarge (Second Admission)	Day 77 (Biopsy Date)
Serum creatinine (mg/dL)	2.6	1.8	1.9	1.64	1.57	1.69	1.8	1.7	2.0
Tacrolimus level (ng/mL)	3.9	5.6	4.1	5.1	7.3	5.2	6.1	9.2	8.5
dd-cfDNA (%)	—	4.3	—	7.8	2.6	2.8	3.5	—	—
Follow-up COVID-19 tests (NP NAT)	—	—	—	Positive	Positive	—	Positive	—	Negative on day 78 postdischarge

COVID-19, coronavirus disease 2019; dd-cfDNA, donor-derived cell-free DNA; NP NAT, nasopharyngeal swab nucleic acid amplification test.
Baseline (1 year prior to presentation): Very low-level DSAs to HLA-DR7 and -DR53. These DSAs were well below a level sufficient to yield a positive flow cytometric crossmatch.
Hospital day 12: Continued presence of DSAs to HLA-DR7 and -DR53. Of concern, DSAs to HLA-DQA2/DQB2 were present at a level compatible with a positive cytotoxicity crossmatch.
Hospital day 14: continued presence of DSA to HLA-DR7, -DR53, -DQA2/DQB2. Of concern, DSAs to HLA-DQA2/DQB9 and -DP20 were present at a level compatible with a positive cytotoxicity crossmatch.
Postdischarge day 70: Continued presence of DSAs to HLA-DR53, -DQA2/DQB9, and -DQA2/DQB2. DSAs to HLA-DR7 and -DP20 had decreased and were below a level considered positive. Collectively, the DSAs were at a level sufficient to yield a positive cytotoxicity crossmatch.
*Note HLA donor-specific antibodies as follows (transplant candidates and their deceased donors were typed for HLA-A, -B, -C, -DR, -DQ, and -DP by reverse sequence-specific oligonucleotide assay (One Lambda LABType), as described by Lucas et al [17]).

precluded further concerns. When DSAs were checked initially and were positive, the clinical suspicion for rejection was low. However, we decided to check plasma dd-cfDNA, initially and serially to determine whether the presence of these antibodies was truly causing a potentially harmful rejection. Given the stable SCr and the very recent COVID-19 infection, we initially opted not to pursue a biopsy because it would not have acutely affected our management of this patient's disease.

The utility of dd-cfDNA in renal transplant recipients during the COVID-19 pandemic has been described in a recent report in which normal results precluded outpatient biopsies in 63% of tested patients [12]. However, this test should not be used to replace an allograft biopsy. The circulating donor-derived cell-free DNA in blood in the Diagnosing Acute Rejection in Kidney Transplant Recipients study validated that plasma levels of dd-cfDNA >1% could discriminate active rejection from no rejection with a high negative predictive value of 84% and a positive predictive value of 61% [13]. However, dd-cfDNA may also be released in response to kidney allograft injury due to acute tubular necrosis [14] and can act as an immunogen stimulating development of DSAs [15].

The greatest challenge resides in managing allograft rejection in kidney transplant recipients with a recent COVID-19 infection, especially in the presence of prolonged viral shedding, which exceeded 90 days in our patient. It remains unclear whether COVID-19 reinfection can occur, but a recent report showed a rapid decay of SARS-CoV-2 antibodies in patients with mild disease [16]. The changes in these antibodies are not yet described in transplant recipients. Therefore, we decided to treat the patient with high-dose intravenous immunoglobulin and restarted low-dose mycophenolate with a plan to increase as tolerated.

The main limitation to our study is the absence of an initial kidney allograft biopsy limiting the conclusion regarding whether the presence of chronic ABMR was a sequel of an acute ABMR following COVID-19 illness or was an ongoing diagnosis prior to COVID-19 infection that was missed because of kidney function stability and lacking an indication to screen for a rejection. The worsening of preexisting DSAs and development of new de novo DSAs during COVID-19 infection make the latter less likely. Nevertheless, the possibility of allograft rejection, whether acute or chronic, should always be considered in high-risk patients with COVID-19 infection whose immunosuppression was reduced in the setting of their acute illness. Using dd-cfDNA is an appealing option for surveillance in such patients. Performing a timely kidney allograft biopsy remains challenging in the COVID-19 era but ideally should not be delayed. Optimal timing for resumption of routine maintenance immunosuppressive regimen, including antimetabolite, following COVID-19 is unclear. However, a resumption sooner rather than later should be strongly considered in patients who are at higher risk of rejection.

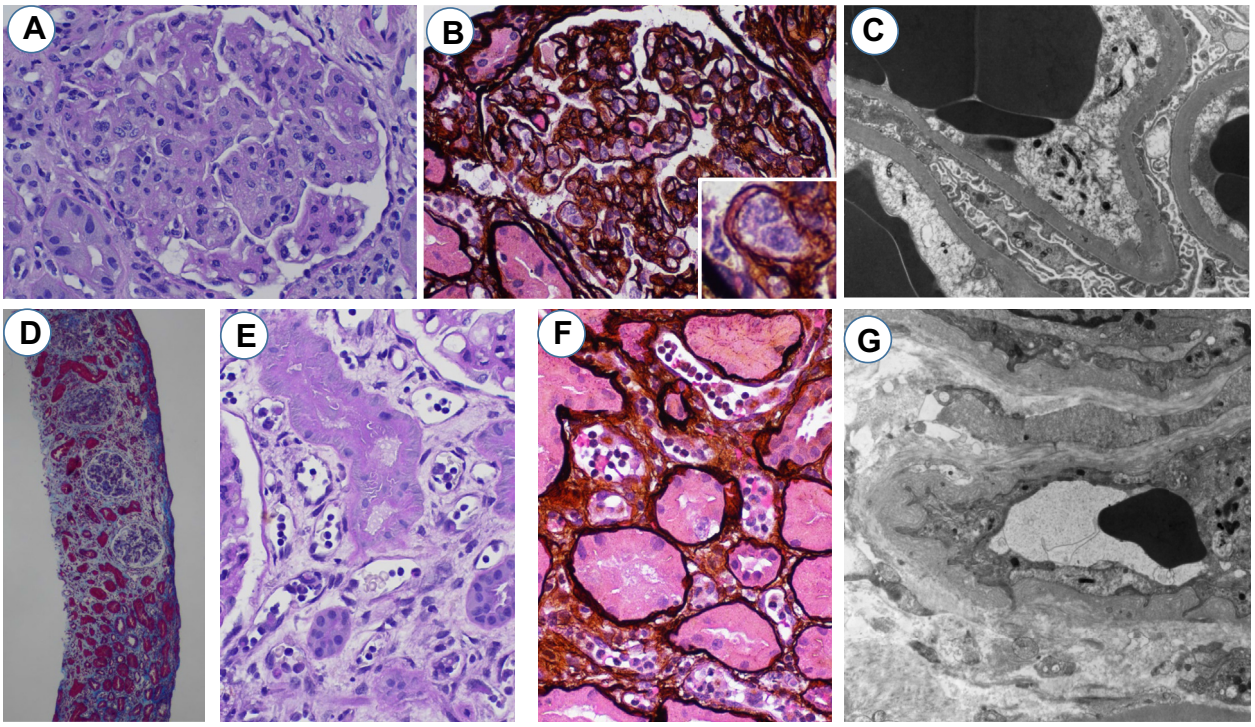

Fig 1. Kidney allograft biopsy findings. **(A)** Glomeruli show hypercellularity with occluded capillary lumina and remodeled thickened walls with mesangial expansion (periodic acid-Schiff stain). **(B)** Capillary walls show segmental duplication (inset) and endocapillary hypercellularity (silver stain). **(C)** Glomerular basement duplication with entrapped cellular debris (electron microscopy). **(D)** Interstitial edema observed on Masson's trichrome. **(E)**, **(F)** Dilated peritubular capillaries with numerous endocapillary leukocytes (periodic acid-Schiff, silver stains). **(G)** Peritubular capillary basement membrane multilayering (electron microscopy).

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