IJKD KIDNEY DISEASES

Antibody-mediated Rejection of Kidney Allografts Following COVID-19: A Report of Two Cases

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Brief Communication

Increased risk of graft rejection could be the consequence of COVID-19 in kidney transplant recipients (KTRs). We report two cases of kidney transplant (KT) with stable graft function who experienced antibody-mediated rejection (ABMR) following recovery from COVID-19. It seems that reduced immunosuppression during the acute illness, is the main explanation for post-COVID-19 ABMR. However, the inflammatory state associated with COVID-19, as well as direct cytopathic effects of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can predispose the kidney allograft to rejection. There is no definite guideline for the modification of immunosuppressives during COVID-19 in kidney transplant recipients. However, re-institution of full-dose immunosuppressives soon after recovery from COVID-19 and frequent outpatient follow-up visits are recommended.

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INTRODUCTION

Several studies have reported the impact of COVID-19 on kidney transplant recipients (KTRs), likely due to the comorbidities and chronic immunosuppression, which is associated with poor patient and graft outcomes.[1-13]

Although the incidence of acute kidney injury following COVID-19 is relatively high in KTRs, only a few cases of biopsy-proven allograft rejection, particularly acute antibody-mediated rejection, have been documented.[14-16] Moreover, the etiology of graft rejection as well as the role of reduced immunosuppression, immune activation due to SARS-CoV2 infection, direct viral cytopathic effects, or other factors on graft function is not elucidated. However, the majority of cases of acute rejections following SARS-CoV-2 infection are reported to be moderate to severe in intensity and require hospitalization.[14-18]

Herein, we present two KTRs with stable graft function, who experienced antibody-mediated allograft rejection following the recovery from

COVID-19.

CASE PRESENTATION

Case 1

A 61-year-old man who received a deceased-donor kidney transplant three years before the presentation was admitted to our hospital due to fever, generalized body pain and significant dyspnea, and the diagnosis of COVID-19 was suspected. His past medical history was positive for diabetes mellitus. On admission, his serum creatinine (sCr) was stable at 1.3 to 1.4 mg/dL and his medication protocol included cyclosporine 75 mg twice daily, CellCept® 1 g twice daily, and prednisolone 5 mg once daily. On primary evaluation decreased O_2 saturation and moderate to severe pulmonary involvement in chest CT-scan were noted (Figure 1). The definite diagnosis of COVID-19 was made with the detection of SARS-CoV-2 on the nasopharyngeal swab. He received intravenous (IV) dexamethasone 8 mg thrice a day which was reduced to 8 mg twice daily on the next days as well as three doses of intravenous β-interferon. Favipiravir, tavanex® and ceftriaxone were latter added to his medications. The dose or frequency of cyclosporine was not changed but mycophenolate mofetil was discontinued during COVID-19 management. Following the clinical improvement of the patient, he was discharged with cyclosporine 75mg twice daily, mycophenolate

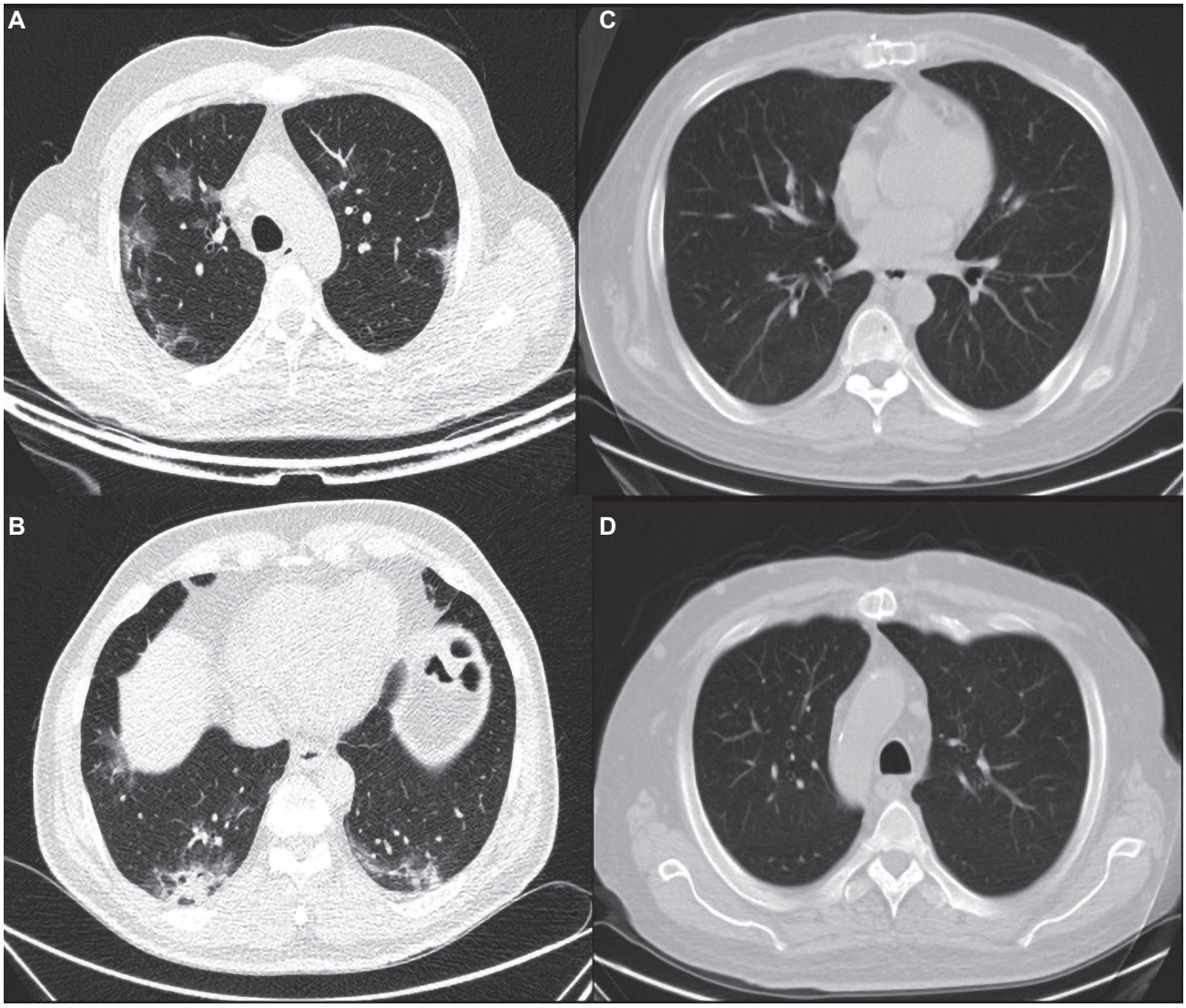

Figure 1. Left panel (A and B) shows moderate pulmonary involvement following COVID-19 infection in a 61-year old kidney transplant recipient (Case 1). Right panel (C and D) shows no pulmonary involvement following COVID-19 infection in a 53-year-old kidney transplant recipient (Case 2).

mofetil 500 mg and prednisone 25 mg daily. Within the first two weeks of COVID-19 recovery, mycophenolate and prednisone was converted to 1 g twice daily and 10 mg twice daily; respectively. The patient's laboratory findings are summarized in Table 1.

At follow-up visits he was asymptomatic and sCr was 1.3 mg/dL. However, sCr increased to 2.7 mg/dL 6 weeks after recovery from COVID-19. Clinical findings were otherwise unremarkable and he was scheduled for kidney allograft biopsy. Light microscopy of the graft biopsy showed an acute antibody-mediated rejection (ABMR) with positive C4d staining (Figure 2). The detailed paraclinical findings are summarized in Table 2. He received methylprednisolone (500 mg, IV, for 3 consecutive days). In addition, intravenous immunoglobulin (IVIG) (50 g) as well as a single dose of rituximab

Table 1. The Laboratory Findings of the Two Patients

	Case 1	Case 2
Laboratory Examinations for COVID-19 Infection		
Absolute lymphocyte count, n/mm^3	1149	660
ESR, mm/h (on admission; at discharge)	50; 25	76; 55
Quantitative CRP (mg/L (on admission; at discharge)	27; 5	35; 27
Creatinine, mg/dL (on admission)	1.3	1.5
LDH, IU/L (on admission; at discharge)	570; 350	980; 556
Ferritin, ng/mL	100	232
IL-6, pg/mL	12	20
Cardiac Troponin I, ng/mL	Negative (< 0.6)	Negative (< 0.6)
D-Dimer, mg/L	Negative (< 0.6)	Negative (< 0.6)

Abbreviations: COVID-19, the coronavirus disease 2019; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase; IL-6, Interleukin 6.

Table 2. Laboratory Findings of the Post-COVID-19 Rejection

	Case 1	Case 2
Viral and Urine Test Results	Negative PCR of BKV & CMV Negative urine culture	Negative PCRs of BK & CMV Negative urine culture
Graft Ultrasound Findings	Abnormal resistance index and increased echogenicity on the graft ultrasound	Abnormal resistance index of kidney allograft
Immunological Assays	Luminex® assay: Positive class I DSA (IgG): (A*24,B*15, 1000<MFI<2000) Negative class II DSA (IgG)	Luminex® assay: Positive class I DSA (IgG): B*15, B*18, B*27, B*35, B*37, B*38, B*39, B*40, B*41, B*42, B*44, B*45 MFI>2000) Positive class II DSA (IgG) (DQA1, DQB1, DRB5; MFI>2000; prozone effect;1/20 diluted serum was prepared)
Kidney Biopsy Findings	Acute ABMR with positive C4d on graft biopsy -acute glomerulitis (endothelial cell swelling; intraluminal neutrophils and mononuclear cells in almost all 10 glomeruli). - No GBM double layering or TMA - about 10% IFTA - cellular debris and lymphocytic tubulitis in some of the tubules - No viral cytopathic effects were seen. - prominent PTCs (> 10%); many of them containing>10 inflammatory cells. - edema with plasma cell infiltration in ~40% of the specimen. - negative Immunofluorescence for IgA, IgG, IgM, complement factor C1q, C3c, fibrinogen, and kappa and lambda light chains	Chronic active ABMR with positive C4d on graft biopsy - glomerulitis (7-8 out of 20 glomeruli) - segmental GBM double layering (in 2-3 glomeruli) - 50% IFTA - moderate lymphocytic tubulitis and cellular debris in preserved tubules. - no viral cytopathic effects or TMA - prominent PTCs (> 10%); some of them containing 5-10 inflammatory cells. - lymphocytic infiltration in about 30% of the specimen. - negative Immunofluorescence for IgA, IgG, IgM, complement factor C1q, C3c, fibrinogen, and kappa and lambda light chains

Abbreviations: COVID-19, the coronavirus disease 2019; Cr, Creatinine; PCR, polymerase chain reaction; ***BK***, BK polyoma **virus**; CMV, cytomegalovirus; DSA, donor-specific antibodies; IgG, IgA, IgM: immunoglobulin G, A, M; MFI, mean fluorescein intensity; C4d$^+$ ABMR, complement component C4d-positive antibody-mediated rejection; IFTA, interstitial fibrosis and tubular atrophy; GBM, glomerular basement membrane; TMA, thrombotic microangiopathy; PTC, peritubular capillary.

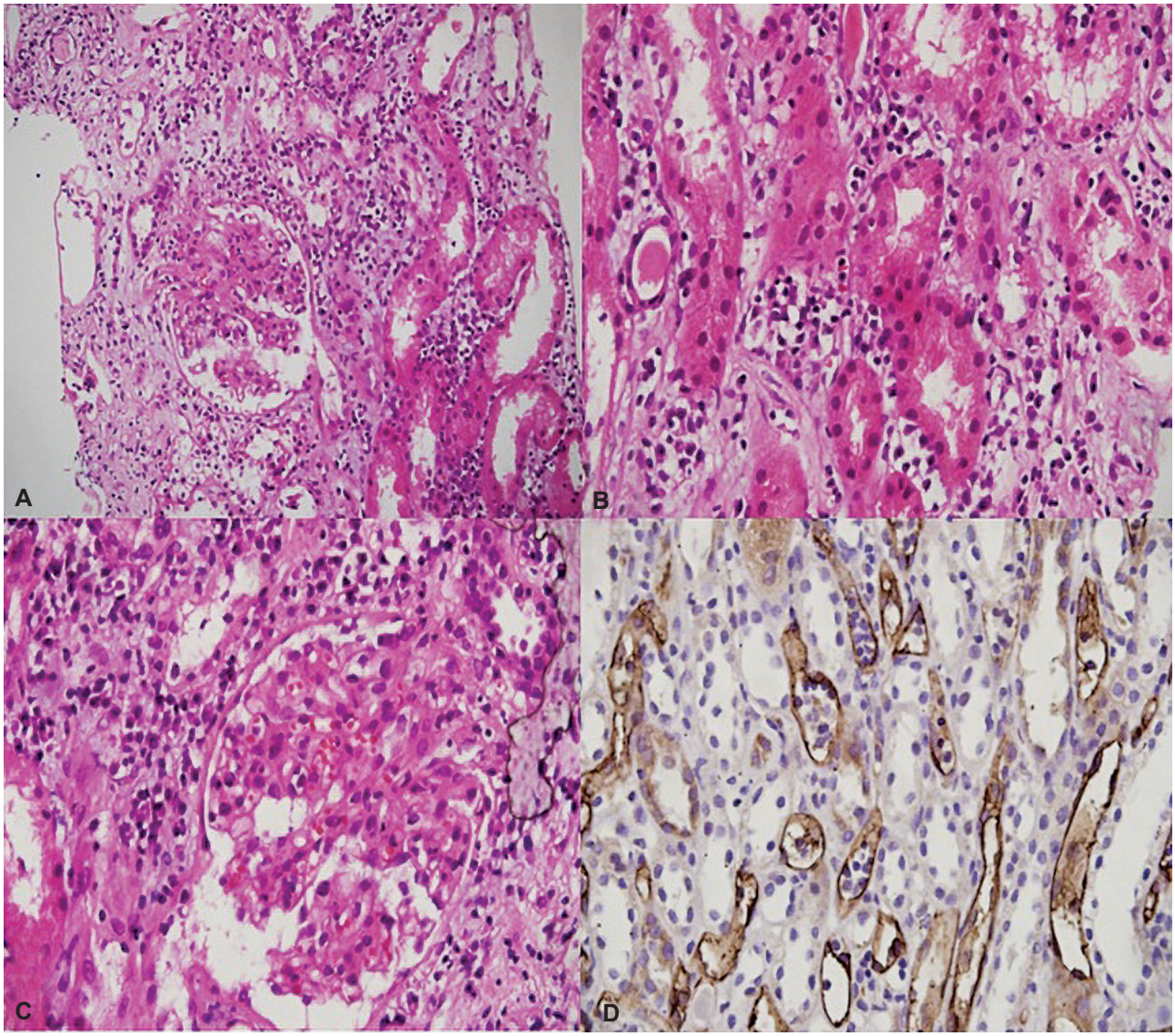

Figure 2. Acute glomerulitis (C) with severe inflammation of peritubular capillaries (A & B) and diffuse C4d staining (D) consistent with acute/active antibody-mediated rejection in a 61-year-old kidney transplant recipient (Case 1) (A: Stained with Periodic Acid–schiff (PAS), ×100; B, C: Stained with Hematoxylin and Eosin (H&E), ×400; D: Immunohistochemical Staining for C4d, ×200).

(500 mg) were administered. Plasmapheresis was not considered given the result of the Luminex® assays for donor specific antibody (DSA). However, the patient received Bortezomib (2.2 mg/d, 4 doses) and was discharged with sCr of 2.8 mg/dL. His sCr was 1.8 mg/dL over his two-year follow-up.

Case 2

A 53-year-old man who received an unrelated-living-donor kidney allograft about two years before the current presentation was admitted with fever, chills and body pain. His past medical history was significant for diabetic nephropathy, coronary artery disease, advanced peripheral neuropathy, and neurogenic bladder requiring intermittent catheterization. The patient's baseline sCr was 1.5 mg/dL and his medication regimen was cyclosporine 75 mg and CellCept® 1 g twice a day, and prednisolone 5 mg daily.

A nasopharyngeal swab turned positive for the corona virus. No significant pulmonary involvement was detected on the chest CT-scan (Figure 1). A more conservative approach was adopted for the second patient. He was isolated at home and advised to maintain strict social distancing. Azithromycin and Acetaminophen was the mainstay of our treatment

measures. Bromhexine syrup was prescribed for symptom relief. Prednisolone dosage, which had been increased to as much as 25 mg/d throughout the COVID-19 illness period, was lowered to 10 mg within two weeks. The previous dosage of 1 g/twice daily of mycophenolate, which had been reduced to 500 mg/twice daily, was resumed following COVID-19 recovery. No changes were made in the dosage or frequency of cyclosporine. The patient's laboratory findings are listed in Table 1.

His sCr was 1.7 mg/dL on the first follow up visit after discharge, which declined to 1.5 mg/dL three days later. After about two months his sCr was reported to be 3.4 mg/dL. The laboratory data is listed in Table 2. Kidney transplant biopsy was compatible with chronic active ABMR with positive C4d staining (Figure 3). Methylprednisolone (500 mg, IV, for 3 consecutive days), IVIG (50 g cumulatively), single dose of rituximab (500 mg) and bortezomib (2.2 mg/d dose) were administered but bortezomib was discontinued due to worsening of neuropathy. In contrast to case 1, five sessions of plasmapheresis were prescribed due to the positive results of Luminex® assay (Table 2). He was discharged from hospital with sCr of 3.2 mg/dL. His sCr was 5.51 mg/dL over his two-year follow-up.

DISCUSSION

In contrast to earlier reports which documented graft dysfunction concurrent with COVID-19 presentation, the patients in our study experienced increased sCr and biopsy proven acute rejection, several weeks after recovering from COVID-19.[15, 16]

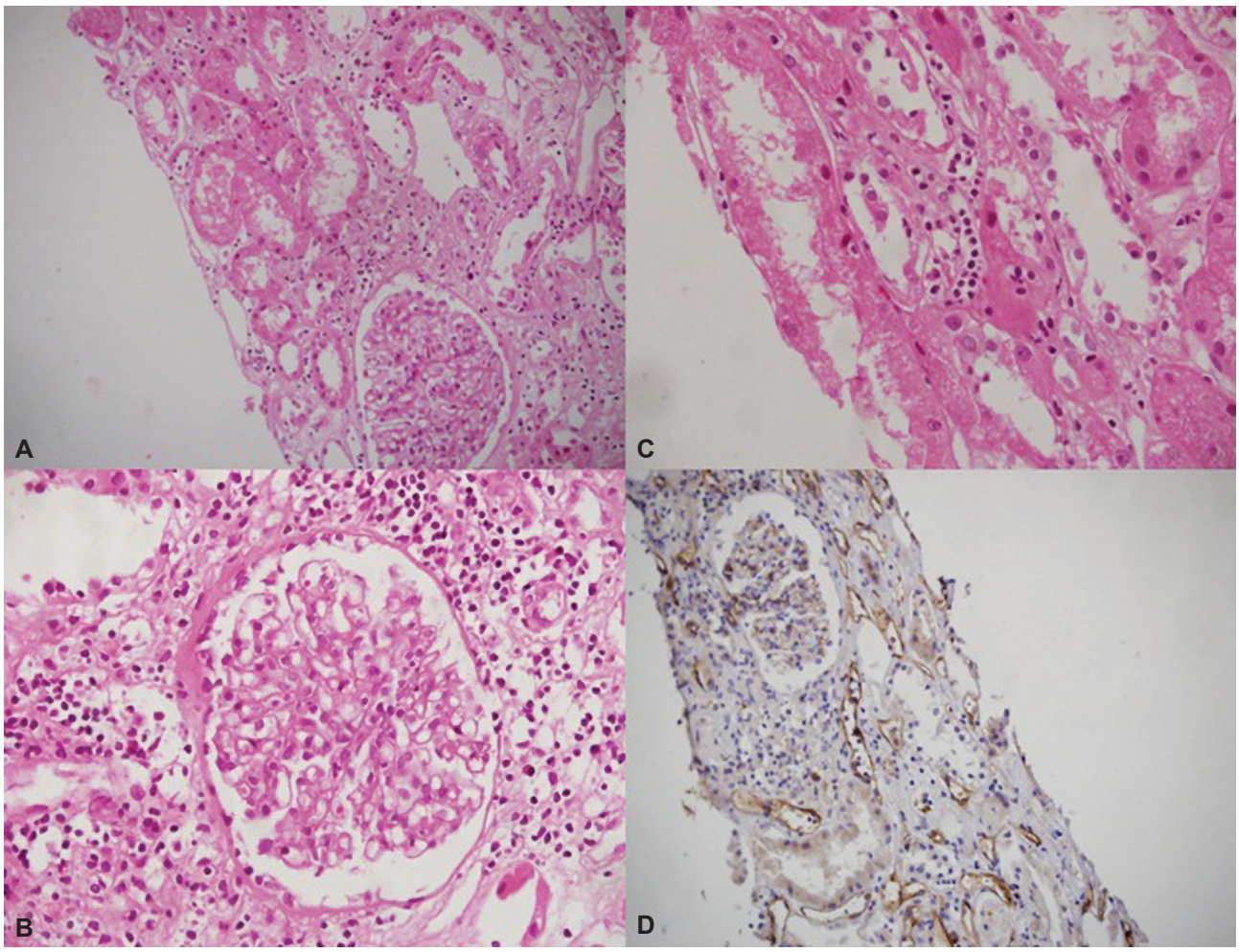

Figure 3. Moderate glomerulitis (B) with moderate inflammation of peritubular capillaries (PTCs) (A, C) and positive C4d staining (IHC) deposition in 40% of the PTCs (D) consistent with chronic active antibody-mediated rejection in a 53-year-old kidney transplant recipient (Case 2) (A: Stained with H&E, ×100; B: Stained with H&E, ×200; C: Stained with H&E, ×400; D: Immunohistochemical Staining for C4d, ×200)

Aziz *et al.* and Abuzeineh *et al.* reported episodes of acute antibody-mediated rejection following discontinuation of immunosuppressive medications during COVID-19.[14,15] The development of the rejection despite resumption of immunosuppressives in our KTRs, can propose the direct cytopathic effects of SARS-COV-2 on the allograft.

As our patients presented with two different COVID-19 clinical course, it could be suggested that the severity of underlying COVID-19 would not necessarily predict post-COVID-19 allograft rejection. Furthermore, it can be hypothesized that donor specific antibody (DSA) titers and the extent of alloreactivity might not certainly correlate with the severity of COVID-19. In addition, antiviral medications and high-dose steroids, used for the treatment of COVID-19, may not be able to prevent graft rejection.

Overall, the reported cases highlight the need for further studies with larger sample size in order to provide a consensus for the prevention and treatment of post-COVID-19 kidney allograft rejection.

AUTHORSHIP CONTRIBUTIONS

Conception and Design of Study

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Analysis and / or Interpretation of Data

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Drafting the Manuscript

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Revising the manuscript critically for important intellectual content: Seyed Amirhossein Fazeli, Miralireza Takyar, Mahmoud Parvin, Abdolreza Haririan, Amirhesam Alirezaei

Approval of the Version of the Manuscript to Be Published

Seyed Amirhossein Fazeli, Miralireza Takyar, Mahmoud Parvin, Abdolreza Haririan, Amirhesam Alirezaei

CONFLICT OF INTEREST

The authors declare no funding was received for this study.

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