CASE REPORT

Novel coronavirus 2019 pneumonia in a kidney transplant recipient

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The COVID-19 pandemic is spreading worldwide and the impact of the disease in transplant patients is evolving. In this case report, we presented a 63-year-old female kidney transplant recipient who presented with dyspnea and cough and was diagnosed with COVID-19 pneumonia. On the fourth day of admission, the patient's condition worsened. Therefore, the immunosuppressive medications were discontinued, and hydrocortisone was started. The patient died on the fifth day.

KEYWORDS

clinical research/ practice, complication: infectious, immunosuppressive regimens – maintenance, infection and infectious agents, infection and infectious agents – viral, infectious disease, kidney transplantation/nephrology

A 63-year-old woman, who was the recipient of a deceased donor kidney transplant 20 years previously, was admitted with dyspnea and cough for 7 days before admission. She did not report headaches, fever, chills, or diarrhea. She had no history of recent travel or close contact with confirmed COVID-19 cases. The only significant previous medical history was hypertension.

Her current medications were mycophenolate mofetil (CellCept) 500 mg twice daily and cyclosporine 75 mg twice daily.

Her physical examination was as follows: temperature: 37.1°C, pulse rate: 80 beats/min, respiratory rate: 22 per min, blood pressure: 120/80 mm Hg, O_2 saturation 83%. There were bilateral coarse crackles in the base of both lungs; other examinations were unremarkable. The laboratory findings showed a total white blood cell count of 9100/mL with polymorphonuclear leukocytes 81.1%, 15.2% of lymphocytes, hemoglobin 8.2 g/dL, platelets 314 000/mL, prothrombin time (PT) 12.5, partial thromboplastin time (PTT) 37, international normalized ratio 1, Na 139, K 4.5, blood urea nitrogen 64, creatinine 2.8 mg/dL, lactate dehydrogenase (LDH) 560 U/L, erythrocyte sedimentation rate (ESR) 81 mm/h, and C-reactive protein (CRP) 60 mg/L. The urine protein dipstick value was 2+.

A chest computed tomography (CT) scan revealed the areas of solid and ground-glass confluent consolidation in both lungs consistent with COVID-19 (Figure 1).

The patient was admitted with an impression of COVID-19, and an oropharyngeal swab test for severe acute respiratory syndrome–associated coronavirus (SARS-CoV-2) was taken. She was sent to the COVID-19 special ward and was given hydroxychloroquine 400 mg single dose orally, Kaletra (lopinavir/ritonavir) 400/100 mg twice daily orally, and oseltamivir 75 mg daily orally. She also received intravenous cefepime 500 mg twice daily.

The pretreatment through the level of cyclosporine was 95 ng/mL, which was in target level range (70-150 ng/mL) recommended by our national protocol. The adjustments based on drug-drug interactions (DDI) were applied and the cyclosporine dose was reduced to 50 mg twice daily. The cyclosporine blood through the level was kept between 90 and 100 ng/mL.

The pretreatment through blood level of CellCept (mycophenolate mofetil) was 1.3 mg/L. We reduced the dose to 500 mg once daily. Given the potential risk of prolongation of QT by both hydroxychloroquine and lopinavir, we performed a daily electrocardiogram to assess the corrected QT interval (QTc).

Echocardiography showed mild pericardial effusion with an ejection fraction of 60%. Abdominopelvic ultrasound revealed increased parenchymal echogenicity in the transplanted kidney.

On the second day of the admission, the patient developed a rise in serum creatinine (3.1 mg/dL) and O_2 saturation dropped to

FIGURE 1 The chest computed tomography of the patient which revealed ground-glass opacities in both lungs [Color figure can be viewed at wileyonlinelibrary.com]

78% with an oxygen mask with a reservoir bag. The patient was alert and communicative, so supportive measures continued, and adjusted-dose vancomycin was added to the medications.

On the fourth day of admission, she developed respiratory distress, increased difficulty in breathing, dyspnea, and oliguria, and she was intubated and underwent 24-hour telemetry. Creatinine increased to 3.4 mg/dL. The CRP level was 78 mg/L, ESR 85, LDH 574, PT 14.5 seconds, PTT 40 seconds, and platelet level was 387 000/mL.

Cellcept and cyclosporine were discontinued, and hydrocortisone 100 mg every 8 hours was started.

On the fifth day, the patient developed foamy bloody discharge through the endotracheal tube, respiratory acidosis, and rise in creatinine (4.4 mg/dL). Unfortunately, the patient became bradycardic and was coded for cardiopulmonary arrest. Cardiopulmonary resuscitation was unsuccessful. The postmortem examination is unlikely to be necessary on a deceased patient with confirmed COVID-19 infection, given the risk of transmission of infectious pathogens during and after the postmortem examination.[1] However, in this case, we determined that a postmortem test should be pursued and asked the relatives for the permission, but the patient's surrogate refused.

The overall clinical presentation, laboratory, and chest CT scan findings of the COVID-19 in the patient discussed above were similar to nontransplant cases. Regarding the treatment, we administered the standard treatment, which has been recommended by the National COVID-19 interim management guidance.

DDI is an important issue in managing a case of COVID-19 with a kidney transplant. Antiviral medications such as Kaletra (lopinavir/ritonavir) may increase the level of cyclosporine. Therefore, dose reduction may be considered.[2,3] Considering the DDI and to avoid toxic drug levels, the dose of cyclosporine had been reduced by 30% in order to keep the cyclosporine in the target level of 70-150 ng/mL recommended by our guideline. We discontinued both immunosuppressants on the fourth day of admission after the patient's condition deteriorated. On the same day, the National COVID-19 guidance announced the recommendation of immunosuppressant withdrawal in severely ill transplant patients.

In China, Zhu et al[4] reported the first renal transplant patient with COVID-19 who was treated successfully with reduced immunosuppressant use and low-dose prednisolone. Moreover, in Italy, Gandolfini and her colleagues reported that their approach for kidney transplant recipients included immunosuppressant discontinuation.[5]

Although reduction or temporary discontinuation of immunosuppressive treatments has been recommended in kidney transplant recipients with viral pneumonia,[6,7] withdrawal of antirejection treatment may exacerbate the cytokine storm activated by COVID-19. The occurrence of cytokine storm could be implied by the high levels of interleukins (IL)-2, -7, and -10, granulocyte-colony stimulating factor, interferon-γ-inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein 1 alpha, and tumor necrosis factor-α.[8,9]

Among these, IL-6 seems to be a leading trigger of the inflammatory cascade, which may increase alveolar-capillary blood-gas exchange dysfunction.[10,11]

In the presented case, we could not assess the existence of a cytokine storm because IL-6 monitoring was not available in our center. However, the development of foamy blood discharge from the lungs, hypoxia, and increased levels of inflammatory markers such as ESR, CRP, and LDH could suggest the presence of the inflammatory response initiated by pro-inflammatory cytokines such as IL-6.

In the presence of a cytokine storm, IL-6-targeting therapies such as tocilizumab may play an important role to control acute respiratory distress syndrome (ARDS) in transplant patients who contracted COVID-19.[5]

In the presented case, it is not clear whether the patient might benefit from discontinuation of immunosuppressant upon admission. According to The Transplantation Society, changes in immunosuppression are not well studied in transplant patients, and adjustment of dose reduction has to balance the consequences of rejection.[12]

The presented patient had a risen creatinine, proteinuria, and increased parenchymal echogenicity in the transplanted kidney at the time of admission, which could be accompanied by a higher risk of rejection with discontinuation of immunosuppressive medication. Therefore, we decided to reduce but not discontinue the immunosuppressants.

Although we reduced the doses of immunosuppressants, nephrotoxicity secondary to DDI could not be ruled out. The other potential explanation of kidney failure of the patient could be direct damage of COVID-19 to the kidney. It has been shown that COVID-19 not only causes pneumonia, but it may also cause direct damage to other organs such as the heart, liver, kidneys, as well as the blood and the immune system.[8,9,13] Therefore, 1 possible explanation of kidney failure, in this case, could be the aggravation of kidney function due to the cytopathic effect of SARS-CoV-2 on kidney.[14]

In summary, we discussed some factors that might contribute to the unfortunate death of the presented patient such as ARDS exacerbated by an inflammatory response and renal failure secondary to

drug nephrotoxicity or direct injury to the kidney by SARS-CoV-2. Moreover, we discussed our treatment strategy in terms of administration of lopinavir-ritonavir as a potentially effective antiviral medication and reduction of immunosuppressants. We tried to balance between the treatment of the patient's COVID-19 infection and the risk of her kidney rejection or provoked inflammatory response. Although the treatment of the patient was not successful, we believe that the reporting of unsuccessful case treatments is crucial in order to obtain the maximum knowledge to protect the population of kidney transplant recipients.

DISCLOSURE

The authors of this manuscript have no conflict of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Hanley B, Lucas SB, Youd E, Swift B, Osborn M. Autopsy in suspected COVID-19 cases. *J Clin Pathol*. 2020;73(5):239-242.
2. Bartiromo M, Borchi B, Botta A, et al. Threatening drug-drug interaction in a kidney transplant patient with Coronavirus Disease 2019 (COVID-19). [Published online ahead of print 2020] *Transpl Infect Dis*. 2020. https://doi.org/10.1111/tid.13286
3. Vogel M, Voigt E, Michaelis H-C, et al. Management of drug-to-drug interactions between cyclosporine A and the protease-inhibitor lopinavir/ritonavir in liver-transplanted HIV-infected patients. *Liver Transpl*. 2004;10(7):939-944.
4. Zhu L, Xu X, Ma KE, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. [Published online ahead of print 2020] *Am J Transplant*. 2020. https://doi.org/10.1111/ajt.15869
5. Gandolfini I, Delsante M, Fiaccadori E, et al. COVID-19 in kidney transplant recipients. [Published online ahead of print 2020] *Am J Transplant*. 2020. https://doi.org/10.1111/ajt.15891
6. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(Suppl 3):S1-155.
7. Kumar D, Michaels MG, Morris MI, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. *Lancet Infect Dis*. 2010;10(8):521-526.
8. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
10. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34(2). https://doi.org/10.23812/CONTI-E
11. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420-422.
12. Guidance on Coronavirus Disease 2019 (COVID-19) for Transplant Clinicians. 2020. https://tts.org/tid-about/tid-presidents-message/23-tid/tid-news/657-tid-update-and-guidance-on-2019-novel-coronavirus-2019-ncov-for-transplant-id-clinicians. Accessed March 16, 2020.
13. Wang D, Hu BO, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061.
14. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97(5):829-838.