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Kidney Transplantation and COVID-19: Two Case Reports

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ABSTRACT

Immunocompromised populations are at great risk of the current 2020 global emergency of coronavirus disease 2019 (COVID-19), and treatment of kidney transplant recipients with COVID-19 is currently not declared. Hence, the purpose of the study is to set a clear treatment regimen. We report here a therapeutic course of 2 patients who underwent transplant surgery in March 2020 and got infected soon after. Since the transplant, these 2 patients have received triple maintenance immunosuppressive therapy with oral tacrolimus, mycophenolate mofetil (MMF), and prednisone, and they have been regularly followed up at our hospital. The tacrolimus trough level was between 10 and 12 ng/mL. After the diagnosis of COVID-19, MMF was stopped and the tacrolimus dose was reduced so that blood level was between 4 and 6 ng/mL. The first patient was a 30-year-old man who, despite being treated with hydroxychloroquine, favipiravir, oseltamivir, and azithromycin therapy, died because of the presence of other comorbidities. The second case was a 58-year-old man who fully recovered from COVID-19 pneumonia with treatment with methylprednisolone, MMF, azithromycin, favipiravir, hydroxychloroquine, and reduction in immunosuppression dosage. This reflects the importance of using glucocorticoids in the treatment of COVID-19 along with other medications and the decreased mortality rate associated with their use.

IN December 2019, novel coronavirus (2019-nCoV) was discovered in Wuhan, China, and spread worldwide [1]. The pandemic highlighted the demand for information concerning coronavirus disease 2019 (COVID-19), which clinically ranges from an asymptomatic manifestation to acute respiratory distress syndrome. Severe COVID-19 infection is associated with factors such as older age (>65 years), hypertension, lactate dehydrogenase (LDH) >445 U/L, and D-dimer >1 mg/L [2]. Additionally, immunocompromised patients are at a higher risk of a poor prognosis for COVID-19 infection [3,4]. In 177 countries, 12,768,307 cases and 556,654 deaths were reported through July 13, 2020. Herein, we present 2 cases of kidney transplant recipients who were infected with COVID-19.

CASE 1

A 30-year-old man presented to the nephrology department with flank pain and weakness on March 23, 2020. Physical examination showed no significant findings except essential hypertension; he had also been diagnosed with chronic kidney disease 1 year prior to this visit. He was taking Amlodipine (10 mg/day) for hypertension. At this time, his serum creatinine was 8.89 mg/dL and estimated glomerular filtration rate was 12 mL/min/1.73 m^2. After discussion with the transplant team, the decision to perform living-related kidney transplantation surgery with his father as the donor was made. The donor-recipient HLA-A, -B, -DR mismatch grade was 3. Preoperative antibody testing showed that the patient was positive for cytomegalovirus IgG. The patient underwent surgery on March 26, 2020. The patient was started on immunosuppressive treatment with tacrolimus (Tac; 8 mg/day), mycophenolate mofetil (MMF; 2000 mg/day), and prednisone (Pred; 20 mg/day) postoperatively. The Tac trough level was 10 ng/mL.

He was discharged 5 days after the operation with signs of a good recovery, at which time the laboratory finding for serum creatinine was 1.2 mg/dL. Eighteen days after transplant surgery he presented to the emergency department with respiratory distress symptoms such as chest pain, dyspnea, and cough. Because of the severity of

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0041-1345/20
https://doi.org/10.1016/j.transproceed.2020.10.051

complaints of a few days' duration, he was admitted directly to the intensive care unit (ICU). There, the diagnosis of COVID-19 was made using real-time polymerase chain reaction (RT-PCR) on a nasopharyngeal swab. In the ICU, he was tachycardic, with rales in the left lung. Chest computed tomography was performed and showed ground glass opacities with consolidation (Figure 1). Urine was brown in color, indicating hemolysis. The patient showed signs of transplant rejection with hemolytic-uremic syndrome (HUS). A clinical diagnosis of acute kidney insufficiency, hematologic insufficiency, sepsis, and multiorgan failure was made.

The patient's lab values were C-reactive protein (CRP), 44.54 mg/L; blood urea nitrogen, 78 mg/dL; serum creatinine, 5.36 mg/dL; total bilirubin, 8.91 mg/dL; direct bilirubin mg/dL, 7.58; and D-dimer: 1300 ng/mL. Intravenous hydration was initiated for the patient, and Tac was stopped. MMF at a lower dose (1000 mg/day) was given along with Pred. For the treatment of COVID-19, he was given favipiravir, hydroxychloroquine, and oseltamivir. Plasmapheresis and IVIg were also started to control the progression of HUS. Despite all efforts, the patient went into cardiac arrest on his third day in the ICU and cardiopulmonary resuscitation (CPR) was initiated. The patient did not respond to CPR and was pronounced dead after 45 minutes of CPR with no response.

CASE 2

A 58-year-old man underwent a living-related kidney transplant for his chronic glomerulonephritis, with his wife as the donor, on March 20, 2020, following 2 months of hemodialysis. During hospitalization, his serum creatinine level was 9.01 mg/dL and estimated glomerular filtration rate was 8 mL/min/1.73 m^2. The donor-recipient HLA-A, -B, -DR mismatch grade was 4. He was discharged 5 days after transplant surgery with normal physics and laboratory signs. His serum creatinine level was 1.4 mg/dL and he received triple maintenance immunosuppressive therapy with oral Tac (6 mg/day), MMF (2000 mg/day), and Pred (20 mg/day). The Tac trough level was 11 ng/mL.

On April 4 he was admitted to the hospital with high-grade fever and myalgia. At admission, the patient had leukopenia, lymphopenia, and thrombocytosis. In addition, he had high levels of acute phase reactant and a mild elevation of CRP. The patient also had D-dimer levels 3 times higher than normal. Lab results were white blood cell count, 1.87 cubic mm; lymphocytes, 0.44 cubic mm; platelets, 488 cubic mm; creatinine, 1.4 mg/dL; CRP, 6 mg/L; ferritin, 233 ng/mL; D-dimer, 689 ng/mL; fibrinogen, 181 mg/dL. A nasopharyngeal swab test was performed and severe acute respiratory syndrome coronavirus 2 was identified by real-time RT-PCR. Chest computed tomography showed findings of viral pneumonia, including ground glass opacities, subpleural lines, septal thickness (Fig 1). Laboratory findings and therapeutic information of both Case 1 and Case 2 can be seen on Table 1.

When the severe acute respiratory syndrome coronavirus 2 diagnosis was confirmed, MMF was discontinued and hydroxychloroquine, prophylactic antibiotics (azithromycin), and methylprednisolone were added to his treatment regimen. Tac, however, was continued at a lower dose with a blood trough level of 4 to 6 ng/mL. The patient was also started on prophylactic enoxaparin because of low fibrinogen levels. Follow-up monitoring in the ICU was not recommended.

In the first 6 days of monitoring the patient, neither clinical nor laboratory findings deteriorated. On day 11, PCR results were still positive. However, on day 21, results were negative, and 72 hours later the second PCR test result was also negative. The patient made a full recovery and was discharged. To date, the patient has been in good health and his serum creatinine level was 1.3 mg/dL.

DISCUSSION

In this article, we discussed 2 patients of different ages who contracted COVID-19 after undergoing renal transplantation surgery. Because of the immunosuppressed state of the patients, more distinct symptoms of COVID-19 infection may be expected, requiring special attention for correct and timely diagnosis. It is postulated that serious consequences of 2019-nCoV are owing to the activation of complement pathways, resulting in increased inflammation and cytokine release as a secondary response to 2019-nCoV. This increase is called a cytokine storm and is usually accompanied by multiple organ failure [5]. Cytokine storm

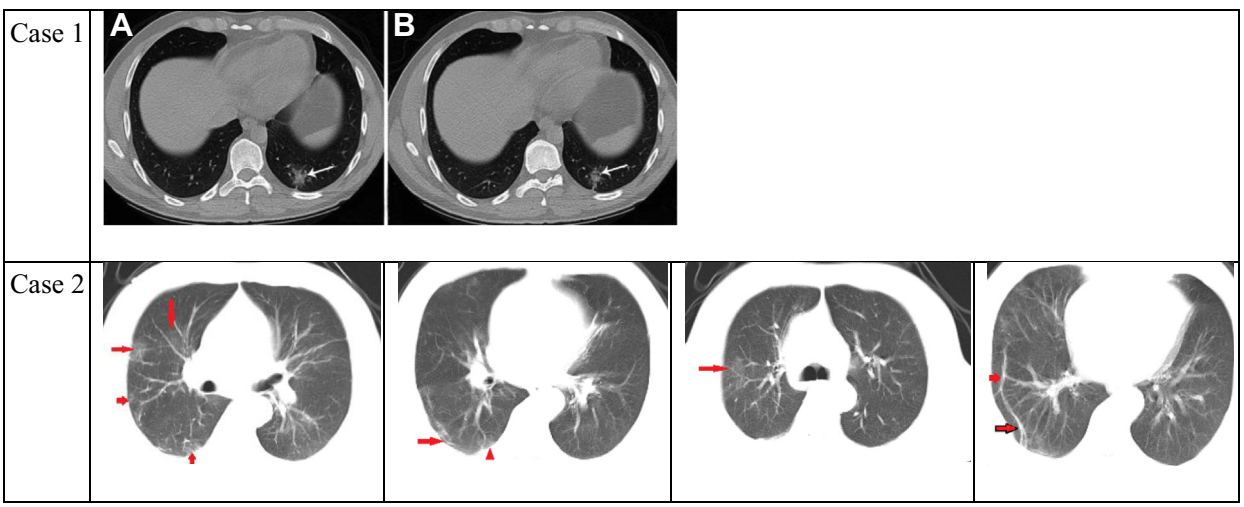

Fig 1. Chest computed tomography images. Case 1: **(A)**, **(B)** Focal, unilateral ground glass opacities with consolidation (arrows) in the left lower lobe posterior basal segment. Case 2: Ground glass opacities, subpleural lines, and septal thickness.

Table 1. Laboratory Findings for 2 Patients Diagnosed With COVID-19

Characteristics	Case 1	Case 2
Age	30	58
Sex	Male	Male
Smoker	No	No
Medical history	Essential (primary) HTN Previous CMV infection GER	Mild mitral and aortic valve insufficiency; Grade II hepatic steatorrhea
Symptoms	Respiratory distress, cough	High-grade fever, myalgia
Labs		
CRP	44.54 mg/L	6 mg/L
BUN	78 mg/dL	28 mg/dL
Creatinine	5.36 mg/dL	1.4 mg/dL
Total bilirubin	8.91 mg/dL	0.9 mg/dL
Direct bilirubin	7.58 mg/dL	0.2 mg/dL
D-dimer	1300 ng/mL	689 ng/mL
WBC	11.23 cubic mm	1.87 cubic mm
Lymphocytes	0.91 cubic mm	0.44 cubic mm
Platelets	53 cubic mm	488 cubic mm
Fibrinogen	184.5 mg/dL	181 mg/dL
Treatment	Favipiravir Hydroxychloroquine Oseltamivir, methylprednisolone	Favipiravir Hydroxychloroquine Azithromycin, methylprednisolone

Abbreviations: BUN, blood urea nitrogen; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GER, gastroesophageal reflux; HTN, hypertension; WBC, white blood cell.

is a major reason for the fatal consequences of COVID-19, and following the levels of LDH, CRP, and ferritin aids in early detection of the storm [6].

In both cases, patients were infected with 2019-nCoV soon after transplant surgery, and both patients were on high-dose immunosuppressant regimens until the diagnosis of COVID-19 was made. After confirmation of a COVID-19 diagnosis, MMF, an immunosuppressant, was stopped as recommended by the available literature [7]. Tac was discontinued in case 1 because of HUS but was continued at a lower dose in case 2.

In case 1, the patient had been experiencing chest pain and dyspnea for many days before he presented to the emergency department. On admission, the patient showed symptoms of not only COVID-19 pneumonia but also aHUS, indicating transplant rejection. aHUS is associated with uncontrollable complement activation, especially anaphylatoxins (C3a, C5a), which leads to faster development of a cytokine storm and, consequently, multiple organ failure [8]. The patient was started on hydroxychloroquine, which suppresses interleukin-6 and tumor necrosis factor-alpha, which can lead to control of the cytokine storm [9]. A severe cytokine storm precipitated by aHUS along with COVID-19 infection in an immunocompromised patient explains the quick progression from mild respiratory symptoms to severe organ failure.

In the earlier periods of the COVID-19 outbreak, and at the time that this case presented, treatment with convalescent plasma (CP) was not recommended for routine use. The use of human CP is currently in the experimental stage. Its mechanism of action involves using antibodies from individuals who have already recovered from COVID-19. The use of human CP for its immunomodulatory effects, in cases of COVID-19, is a safe choice, especially because of the lack of a vaccine [9]. Treatment with human CP has been known to reduce the rate of mortality in viral respiratory infections [10]. The use of human CP could possibly have aided in the treatment of this patient.

Furthermore, starting this patient on tocilizumab, an interleukin-6 blocker, may have improved the patient's prognosis. The addition of tocilizumab to the treatment plan for COVID-19 has shown great results, reducing the mortality rate and even ICU admissions [11,12]. However, the use of the drug was not routinely recommended at the time of this case.

In case 2, the patient presented to the emergency department soon after he developed a fever, prompting an early diagnosis of COVID-19. This allowed for appropriate treatment to be initiated for a better prognosis. Lack of severe disease manifestations in this patient can also be credited to use of methylprednisolone along with hydroxychloroquine.

In conclusion, monitoring of LDH and ferritin is crucial in immunosuppressed patients to detect the development of cytokine storm, which can prove to be fatal for patients infected with 2019-nCoV. We reported that despite differences in the clinical progression of COVID-19 in both patients, discontinuing MMF and continuing Tac proved to be beneficial overall. It can be hypothesized that the use of hydroxychloroquine alone is not enough, and it should be administered along with methylprednisolone for better prognosis; thus, we provide a reference case for treating immunocompromised patients infected with 2019-nCoV.

Antivirals may also be added to the treatment regimen; however, data supporting their use are limited.

CONCLUSION

In conclusion, COVID-19 can be fatal for immunosuppressed patients. We present 2 patients, both of whom were infected with 2019-nCoV soon after kidney transplant surgery in March 2020. We lost the patient in case 1 because of the presence of aHUS, a previous cytomegalovirus infection, and late diagnosis. The patient in case 2, however, was diagnosed early and received early treatment and recovered fully. We report that an early diagnosis and combination therapy with hydroxychloroquine and glucocorticoids proved beneficial for overall prognosis. These cases provide a template for the treatment of patients with and without comorbidities.

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