Oligosymptomatic Kidney Transplant Patients With COVID-19: Do They Pose a Risk to Other Recipients?

Burak Kocak[a], Emre Arpali[a,*], Basak Akyollu[a], Berna Yelken[a], Suda Tekin[b], Mehmet Kanbay[c], Aydin Turkmen[a], and Munci Kalayoglu[a]

[a]Department of Organ Transplantation, Koç University Hospital, İstanbul, Turkey; [b]Department of Infectious Disease, Koc University Hospital, İstanbul, Turkey; and [c]Department of Nephrology, Koc University Hospital, İstanbul, Turkey

ABSTRACT

The clinical course of viral infections in patients under immunosuppression can be atypical and/or fatal if not diagnosed and treated appropriately. The coronavirus disease 2019 (COVID-19) may also have an atypical presentation. Contrary to the general opinion, transplant patients may be asymptomatic or oligosymptomatic, which could be a risk factor for underdiagnosis and the dissemination of this viral disease.

This study presents the clinical features of 2 oligosymptomatic kidney transplant patients diagnosed with COVID-19. We suggest that new screening algorithms for COVID-19 should be reconsidered for the transplant patient population.

THE novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been identified as the causative agent for coronavirus disease 2019 (COVID-19) [1,2]. The clinical course of the disease is usually characterized by fever and respiratory symptoms such as cough and dyspnea; however, in some cases, the disease can progress to severe viral pneumonia and respiratory failure, necessitating intubation [1,3,4].

It is well-known that viral infections may cause atypical symptoms and signs in transplant patients because of chronic immunosuppression. Although some data regarding the clinical manifestations and course of COVID-19 in transplant population have been published, a standardized algorithm that defines risk factors, diagnosis, and treatment options has not been revealed. This study presents 2 kidney transplant patients with COVID-19.

CASE REPORTS
Case 1

A 28-year-old woman previously referred to our department with a diagnosis of end-stage renal disease secondary to a lupus-like syndrome, who underwent a preemptive kidney transplant from her mother 6 months previously, presented to the transplant clinic with symptoms of rhinorrhea, sore throat, malaise, and subfebrile fever self-measured at home shortly after a vacation to England. Her chart revealed that she was treated in the past with cyclophosphamide, followed by a regime consisting of mycophenolate mofetil (MMF) and oral corticosteroids for her primary disease. She received an induction therapy of antithymocyte globulin during her transplant, followed by a triple maintenance therapy of oral tacrolimus (Tac), MMF, and prednisone (Pred). She was also treated with only 2 courses of eculizumab for transient thrombotic microangiopathy, which she experienced in the early post-transplant period. MMF was discontinued in the clinic follow-up because of recurrent leukopenia, and she had been on dual maintenance therapy, which consisted of Tac and 10 mg/d Pred.

On her first visit to our transplant clinic, all vital signs including respiratory rate and oxygen saturation on room air were within normal ranges. Physical examination was unremarkable except for hyperemia of the tonsils and pharyngeal mucosa. Blood test results were unremarkable except for the total lymphocyte count, which was $300/\mu$, and the c-reactive protein (CRP) level, which was slightly elevated to 5.7 ng/L. Laboratory studies also showed a serum creatinine level of 0.92 mg/dL, a glomerular filtration rate of 85 mL/min, a white blood cell count of $3120/\mu l$, and a Tac level of 7.23 ng/mL, all within normal limits. Chest x-ray revealed no abnormal findings, and her swabs tests were all negative for influenza virus A/B and respiratory syncytial virus. A swab test for COVID-19 was not obtained, as the patient had not met the institutional criteria for testing. These criteria were a reported body temperature over 38°C, cough and/or respiratory distress, and an epidemiologic risk of contact. The patient was discharged home with a prescription for oral amoxicillin and isolation instructions.

*Address correspondence to Emre Arpali, Organ Transplant Center, Koç University Hospital, Topkapı Mahallesi, Davutpaşa Cd. No. 4, 34010 Zeytinburnu, İstanbul, Turkey. Tel: + 90 533 644 8968. E-mail: arpemre@gmail.com

The following day, the patient was readmitted to the hospital reporting a high fever of 38°C self-measured at home. Physical examination was unremarkable with all vital signs being normal. Laboratory studies provided no additional information. Nasopharyngeal swab tests (SARS-CoV-2 polymerase chain reaction, RealStar, Altona Diagnostics, Hamburg, Germany) for COVID-19 were obtained, and she was sent home on oseltamivir treatment per infectious disease recommendations with strict isolation precautions.

Six days later, her COVID-19 test came back positive. No elevated body temperature or worsening of the symptoms were recorded in the meantime. Nevertheless, she was admitted to the hospital for monitoring and further testing. Her physical examination was unremarkable, and blood tests and chest computed tomography (CT) revealed no pathologic changes. After a 24-hour observation in the hospital, she was discharged home. Her control test for COVID-19 was negative 7 days after discharge. She has completed 27 days of an uneventful recovery period so far with no complaints at home.

Case 2

A 56-year-old woman who had a kidney transplant from her daughter 3 months previously presented to our emergency department with diarrhea lasting for 3 days. Her medical history was unremarkable except for hypertension for 15 years, and her blood pressure was reported to be under control currently with amlodipine and nebivolol. Deterioration in her kidney function was established incidentally 2 years ago during a routine examination. However, a specific underlying cause for kidney failure could not be found. Routine preoperative evaluation before the transplant was unremarkable.

She underwent a kidney transplant with an induction therapy of antithymocyte globulin, followed by triple maintenance therapy, which included oral Tac, MMF, and Pred. Her postoperative period was uncomplicated, and the patient was discharged on post-op day 4.

Her physical examination was unremarkable with normal vital signs, including a body temperature of 36.4°C. In her initial blood test results, the patient's creatinine level was slightly elevated to 1.54 mg/dL from a baseline value of 1.2 mg/dL, the white blood cell count was 9,990/μl, the total lymphocyte count was 600/μ, and her CRP level was elevated at 49.5 ng/L. Stool microscopy was negative for blood and white blood cells. Metronidazole was started empirically, and the patient was sent home with instructions for adequate hydration.

Three days later, the patient was readmitted with a history of worsening diarrhea and a reported body temperature of 38°C at home. During this encounter, her vital signs revealed a body temperature of 37.4°C, a pulse rate of 87/min, a respiratory rate of 22/min, blood pressure of 134/87 mm Hg, and an oxygen saturation of 96% on room air. A thorough physical examination of the chest and abdomen was performed, and no pathologic findings were noted. According to the blood test results at this admission, the patient's creatinine level was elevated to 2.26 mg/dL, the white blood cell count was 6,160/μl, the total lymphocyte count was 700/μ, and her CRP level was elevated at 76.1 ng/L. Her Tac level was 40 ng/mL. Given the atypical course of COVID-19 in transplant patients, we collected nasopharyngeal swab tests for COVID-19 and ordered a chest CT scan. The chest CT scan revealed bilateral, multifocal ground glass opacities, suggesting coronavirus infection. The patient was hospitalized for close monitoring and further testing. Tac and MMF were discontinued. She was kept on only

Pred 10 mg/d. Hydroxychloroquine was started for COVID-19, and ceftriaxone treatment was added for the prevention of secondary bacterial infections. The COVID test came back positive the following day after hospitalization.

During this admission, the patient's vital signs remained stable without any decline in oxygen saturation on room air. Her diarrhea and fever improved gradually in 2 days. She was discharged home with isolation instructions after a 3-day hospital stay. Currently, the patient has been in good condition at home without any complaints for 20 days.

DISCUSSION

The clinical course of viral infections in transplant patients has always been a source of concern among physicians. As these patients are under chronic immunosuppression, viral infections can easily progress to become fatal. The clinical manifestations of COVID-19 in the general population were reported to include "asymptomatic carrier status," "mild flulike disease," "acute respiratory disease," and "severe disease." Of the cases from the general population, 16% to 18% were reported to be severely ill patients according to the previous reports [5,6]. However, not much data exist in the literature regarding the clinical presentation and course of COVID-19 in kidney transplant patients.

On a theoretical level, renal transplant patients may not show appropriate immune response to clear the SARS-CoV-2 virus, and COVID-19 may have more grave clinical presentations than do the general population. Reports on the clinical course and treatment of renal transplant patients with COVID-19 are scarce and mostly focused on the treatment of symptomatic patients. The most common symptoms of these reported patients were high fever and respiratory symptoms. All these patients with overt disease required treatment and close monitoring (Table 1) [7–11].

On the other hand, in addition to their immunosuppressive effects, the drugs used in kidney transplantation may alter the course of COVID-19 through different pathways. Tac and low-dose steroids were shown to have antiviral effect on some of the human coronaviruses [12]. Nevertheless, their benefit in COVID-19 has not been verified.

The exaggerated activation of the complement system and inappropriate cytokine response were hypothesized to cause the critical illnesses reported in COVID-19 [13,14]. Corticosteroids can mitigate systemic symptoms and can alleviate the alveolar exudation caused by the cytokine storm [15]. Thus, kidney transplant patients who are on steroids and other immunosuppressive drugs may exhibit unusual clinical courses resulting from coronavirus infection.

Our 2 patients presented to the hospital with symptoms not suggesting COVID-19, and they were ineligible to be screened for SARS-CoV-2 according to the national outbreak management case definition, which was "a reported body temperature over 38°C" or "cough and/or respiratory distress" and "epidemiologic risk of contact. Therefore, both patients were treated accordingly and sent home during their first presentations. They could be tested for COVID-19 only after their disease had progressed and

Table 1. Demographic Data, Clinical Manifestations, Treatment Choices and Clinical Courses of the Transplant Patient With COVID-19 (Flulike Symptoms Include Cough and High fever in Addition to Rinore)

Patients	Age	Sex	Comorbidities	Manifestation	Antiviral Treatment	Intubation	Outcome
Our first Pt	28	Female	None	Mild flulike symptoms	Oseltamivir	No	Recovered
Our second Pt	56	Female	HT	Diarrhea	Hydroxychloroquine	No	Recovered
Pt-1[8]	52	Male	N/A	Viral pneumonia	IVIG, interferon α	No	Recovered
Pt-2[7]	50	Male	Third kidney Tx, history of PTLD	Viral pneumonia, Gastroenteritis	Lopinavir/ritonavir, hydroxychloroquine, interferon β	Yes	Stabilized
Pt-3[9]	75	Male	N/A	Viral pneumonia	Lopinavir/ritonavir, hydroxychloroquine	No	Exitus
Pt-4[9]	52	Female	N/A	Viral pneumonia	Lopinavir/ritonavir, hydroxychloroquine, colchicine	No	Stabilized
Pt-5[10]	38	Male	None	Viral pneumonia	Oseltamivir	No	Recovered
Pt-6[10]	64	Male	History of Bladder Cancer	Viral pneumonia	Oseltamivir, IVIG	No	Respiratory Symptoms worsened
Pt-7[10]	37	Female	HT	Viral pneumonia	Oseltamivir, IVIG	No	Symptoms Resolved
Pt-8[10]	47	Male	None	Viral pneumonia	Oseltamivir	No	Symptoms Resolved
Pt-9[10]	38	Male	HT, DM	Viral pneumonia	Oseltamivir	No	Recovered
Pt-10[11]	48	Male	HT	Flulike symptoms	None	No	Recovered
Pt-11[11]	67	Female	DM	Viral pneumonia, ARDS	None	Yes	Exitus
Pt-12[11]	54	Female	DM	Viral pneumonia, ARDS	Oseltamivir	Yes	Stabilized
Pt-13[11]	65	Male	HT	Viral pneumonia	None	No	Symptoms resolved
Pt-14[11]	69	Female	DM, HT	Viral pneumonia	None	No	Symptoms resolved
Pt-15[11]	54	Male	Hereditary hemolytic anemia	Flulike symptoms	None	No	Stabilized
Pt-16[11]	45	Male	HT	Viral pneumonia	None	No	Symptoms resolved

Abbreviations: ARDS, acute respiratory distress syndrome; DM, diabetes Mellitus; HT, hypertension; IVIG, intravenous immunoglobulin therapy; Pt, patient; PTLD, post-transplant lymphoproliferative disease; Tx, transplantation.

after they had presented to our clinic with a history of elevated body temperature at home.

Although most of the patients were reported to present with similar symptoms, such as cough and high fever, our first patient presented with mild flulike symptoms, and the second patient had only diarrhea. Both patients denied any history of fever at their first admission.

The sensitivity of the SARS-CoV-2 polymerase chain reaction tests varies depending on the collection sites of the specimens [16]. The percentages of positive test results were reported to be 63% and 32% from nasal swabs and pharyngeal swabs, respectively [16]. According to our un-published data of the COVID-19 patients diagnosed based on chest CT and clinical findings, 45% was reported to have a positive nasopharyngeal swab test. So far, 4023 samples were analyzed in our institution's laboratory, and 18.5% of the all samples were positive.

Considering the clinical course of our transplant patients, the importance of oligosymptomatic or asymptomatic organ recipients is 2-fold.

First, the extent of symptoms and complaints may differ in immunocompromised patients from that of the general popu-lation, particularly in oligosymptomatic patients. This may cause a delay in the diagnosis of COVID-19 and early treatment.

Second, immunocompromised but oligosymptomatic transplant patients as possible carriers might be exception-ally contagious to the other transplanted patients, they come across in the hospitals and the community. Consequently, a new testing policy other than the national pandemic screening protocol for the general population is needed. Thus, we strongly suggest that every transplant recipient who presents to the hospital for any reason be tested for COVID-19 regardless of symptoms.

CONCLUSIONS

The transplant community should discuss the validity of the case definition for screening COVID-19 in transplant pa-tients, which is established in many countries for the general population.

REFERENCES

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.

[2] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: im-plications for virus origins and receptor binding. Lancet 2020;395(10224):565–74.

[3] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061–9.

[4] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13.

[5] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20.

[6] Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020;7(1):11.

[7] Guillen E, Pineiro GJ, Revuelta I, Bodro M, Moreno A, Campistol JM, et al. Case report of COVID-19 in a kidney trans-plant recipient: does immunosuppression alter the clinical presen-tation [e-pub ahead of print]? Am J Transplant, https://doi.org/10.1111/ajt.15874, [accessed 09.04.20].

[8] Zhu L, Xu X, Ma K, Yang I, Guan H, Chen S, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression [e-pub ahead of print]. Am J Transplant, https://doi.org/10.1111/ajt.15869, [accessed 17.03.20].

[9] Gandolfini I, Delsante M, Fiaccadori E, Zaza G, Manenti L, Antoni AD, et al. COVID-19 in kidney transplant recipients. Am J Transplant 2020. https://doi.org/10.1111/ajt.15891, [accessed 31.03.20].

[10] Zhang H, Chen Y, Yuan Q, Xia QX, Zeng XP, Peng JT, et al. Identification of kidney transplant recipients with coro-navirus disease 2019. Eur Urol, https://doi.org/10.1016/j.eururo.2020.03.030, [accessed 02.04.20].

[11] Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. Kidney Int 2020;97(6):1076–82.

[12]] Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, et al. Associations between immune-suppressive and stim-ulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience 2020;14(1022).

[13] Smits SL, de Lang A, van den Brand JMA, Leijten LM, van Ijcken WF, Eijkemans MJC, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog 2010;6(2):e1000756.

[14] Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, Leist SR, et al. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. mBio 2018;9(5):e01753-18.

[15] Lansbury LE, Ridrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza: an updated Cochrane systematic review and meta-analysis. Crit Care Med 2020;48(2):e98–106.

[16] Wang W, Xu Y, Gao R, Lu R, Han R, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323(18):1843–4.