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### **Two distinct cases with COVID-19 in kidney transplant recipients**

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**Abbreviations:** COVID-19, coronavirus disease; KT, Kidney transplant; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; real-time polymerase chain reaction, RT PCR; uPCR, urine protein to creatinine ratio; CRP, C-reactive protein; antibody-mediated rejection, AMR; CT, computed tomography.

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## **Abstract**

The fatality of novel coronavirus disease (COVID-19) is precipitously increased in patients with underlying comorbidities or elderly people. Kidney transplant (KT) recipients are one of the vulnerable populations for infection. COVID-19 infection in KT recipients might be a complicated and awkward situation, but there has been a lack of reports concerning this group. Herein, we demonstrated two distinct cases with different clinical progress. The first case was a 36-year-old man who underwent KT 3 years ago. He was diagnosed with COVID-19 expressing relevant symptoms. Following administration of lopinavir/ritonavir and hydroxychloroquine with reduced immunosuppressant, he recovered from COVID-19. However, the unexpected fluctuations in tacrolimus trough levels needed to be managed because of drug-to-drug interaction. The second case was developed in a 56-year-old man without any symptoms. He took the second KT from an ABO-incompatible donor 8 years ago. He was diagnosed with COVID-19 by screening due to exposure history. During the hospitalization period, the chest infiltrative lesion showed a wax and wane, but he successfully recovered by hydroxychloroquine with azithromycin. These apparently different cases suggest that assertive screening and management could improve the clinical course. In addition, antiviral agents should be used cautiously, especially in patients on calcineurin inhibitors.

## Introduction

Novel coronavirus disease (COVID-19) was initially developed in Wuhan, China, in December 2019 (1-4). South Korea is one of the earliest experienced countries for the COVID-19 outbreak. Until 04 April, 455,032 people were tested, and 10,156 were diagnosed as COVID-19 positive. It is rapidly spreading regardless of nation, but there is still no specific treatment regimen, especially for the immunocompetent population.

South Korea ranked 2<sup>nd</sup> in the average yearly change in kidney transplantation (KT) rate with a 2.1% increase per year (5). KT is the best treatment strategy for patients with end-stage renal disease (ESRD). However, balancing between the infection and rejection is a critical issue for improving long-term outcomes in KT. Because the overall immunity is decreased due to life-long taking immunosuppressant drugs, KT recipients are vulnerable to infections (6). In addition, all recipients show different clinical manifestations with various underlying diseases and immunosuppressant regimens. Therefore, it is more challenging to propose proper management guidelines for infectious diseases in these patients than in the general population. However, the accumulation of diverse experiences could help to improve the overall outcomes; thus, we aimed to share our experience with two recipient cases with COVID-19 showing distinct clinical courses.

### Case 1.

A 36-year-old man was admitted to our hospital with fever, cough, rhinorrhea, diarrhea, and decreased urine output. He was diagnosed with ESRD due to focal segmental global sclerosis and received living unrelated donor KT in April 2016. The donor-recipient HLA-A, -B, -DR mismatch grade was 5. The maintenance immunosuppressants were long-acting tacrolimus (2 mg, q24hours [hr]), mycophenolate mofetil (MMF) (500 mg, q12hr), and prednisolone (10 mg, qd) (Figure 1-A). At the latest follow-up date on the 19<sup>th</sup> of February 2020, the level of serum creatinine (sCr), estimated glomerular filtration rate (eGFR) and tacrolimus trough was 1.47 mg/dL, 54.5 mL/min/1.73 m<sup>2</sup>, and 3.8 ng/mL, respectively. In addition, there was no proteinuria.

On the 12<sup>th</sup> of March 2020, he felt a febrile sensation with coughing and rhinorrhea. After 2 days, diarrhea occurred, and urine volume decreased. He reported no history of travels abroad or exposure to infected or suspected patients of contagious COVID-19. On the 16<sup>th</sup> March 2020, he visited the hospital and performed real-time polymerase chain reaction (RT-PCR) for COVID-19 by nasopharyngeal swab. After 1 day, he was diagnosed with COVID-19 and was admitted to the hospital. His vital signs were stable, with mild fever at 37.6 °C when he was admitted. The initial laboratory findings showed decreased lymphocyte count, increased C-reactive protein (CRP), sCr level, and urine protein to creatinine ratio (uPCR) (Table 1).

Chest X-ray showed subsegmental atelectasis on both lower lung field and peribronchial infiltration in the left upper lobe (Figure 2). On hospital day 2, the fever spiked to 38.5 °C, and we decided to discontinue the MMF and to start with a lopinavir/ritonavir (400/100 mg, bid). Two days later, the tacrolimus trough level abruptly increased to 16.5 ng/mL. Thus, we discontinued tacrolimus and changed prednisolone to intravenous methylprednisolone (30 mg, qd). After discontinuation of tacrolimus, the trough level peaked at 24.6 ng/mL and started to decrease, and it took 10 days to reach the therapeutic range (Figure 1-A). From hospital day 5, diarrhea and chest discomfort were relieved, and kidney function was recovered with decreased uPCR. We reduced the dose of prednisolone by changing from intravenous to per-oral administration on hospital day 8. Two days later, fever and diarrhea redeveloped, and deterioration of allograft function and chest infiltrate were reagravated (Figure 2). Following the rechallenge of methylprednisolone with increased dose and hydroxychloroquine, the symptoms were relieved, and kidney function was stabilized again (Table 1). On hospital day 13, we discontinued lopinavir/ritonavir. Day after we changed methylprednisolone to prednisolone. From hospital day 18, we resumed tacrolimus from 0.5 mg q24hr. After that, the clinical course was maintained stable; hydroxychloroquine was discontinued on hospital day 23. During in-hospital days, he did not show hypoxia in room air, and peripheral capillary oxygen saturation was maintained above 95%. Finally, chest lesion was significantly improved with stable kidney function; COVID-19 was not detected in RT-PCR in two consecutive days.

### **Case 2.**

A 56-year-old man was transferred from a local hospital with cough and sputum. He was diagnosed with ESRD due to type 2 diabetes mellitus in 2003. He underwent deceased donor KT in October 2004. After 4 years, allograft dysfunction progressed to ESRD and he returned to hemodialysis. In December 2011, he took ABO-incompatible KT from his wife. The donor-recipient HLA-A, -B, -DR mismatch grade was 6. Three months post-transplantation, he developed candida esophagitis and cytomegalovirus gastritis. In addition, One-year post-transplantation, he was diagnosed with acute antibody-mediated rejection (AMR) and treated with steroid pulse therapy, plasma exchange, and rituximab 375 mg/1.73 m<sup>2</sup>. Thereafter, he regularly followed-up with stable kidney function, and the latest sCr and eGFR values were 1.97 mg/dL and 36.9 mL/min/1.73 m<sup>2</sup>, respectively. The maintenance immunosuppressants used were long-acting tacrolimus (4 mg, q24hr), MMF (500 mg, q12hr), and prednisolone (10 mg, qd) (Figure 1-B). The latest tacrolimus trough level was 8.6 ng/mL.

On the 1<sup>st</sup> of March 2020, he visited a screening hospital owing to contact history with a COVID-19 confirmed patient. He did not have any symptoms, but the result of RT PCR assay via nasopharyngeal swab for COVID-19 was positive. He was admitted to the regional hospital and took supportive care without

taking any antiviral agents or antibiotics. However, during the in-hospital period, he experienced flank pain with vesicles and was diagnosed with herpes zoster. He took famciclovir for a week. After discontinuation of the drug, he had cough and sputum. Since ground-glass opacity was newly developed in the chest computed tomography (CT) (Figure 3) with an increased level of CRP, he was transferred to our hospital. On the 18<sup>th</sup> of March 2020, he was admitted with a stable vital sign, and laboratory results were not significantly different from the latest follow-up data before the diagnosis of COVID-19 (Table 1). Day after admission, we discontinued MMF and maintained tacrolimus and prednisolone. On the same day, hydroxychloroquine (400 mg, qd) was administered (Figure 1-B). On hospital day 9, his vital signs were stable, coughing was relieved, but the chest infiltrative lesion was slightly aggravated (Figure 3) and he was still positive for COVID-19 on RT-PCR assay. We added azithromycin (500 mg, qd) to hydroxychloroquine (7). During in-hospital days, he often suffered from coughing; his peripheral oxygen saturation was maintained above 95% without oxygen supply. Finally, the respiratory symptoms were relieved and lung lesions were slightly improved on chest X-ray (Figure 3); COVID-19 was not detected in RT-PCR assay in two consecutive times at hospital day 17 and 18.

## Discussion

COVID-19 infection in KT recipients is rarely reported, but it brings lots of things to consider. We diagnosed two recipients with COVID-19 using an aggressive screening strategy. The first case showed typical clinical features, including cough, rhinorrhea, and diarrhea. Meanwhile, the second case did not show any clinical symptoms when he was diagnosed with COVID-19. Although there is no established treatment strategy, we used lopinavir/ritonavir and hydroxychloroquine for the first case and hydroxychloroquine with azithromycin for the second case. Finally, both cases were fully recovered from COVID-19.

Following the enormous advance in the understanding of the immune responses to a transplanted organ, KT outcomes were significantly improved (8). Nevertheless, infectious disease, which was one of the challenging issues in this population, should be cautiously monitored in light of the suppressed immunity. Although the second case did not experience any symptoms at the time of diagnosis, his clinical feature was eventually aggravated, and he needed medical intervention. This suggests that assertive screening and proper management might have a positive effect on improving the clinical outcome, especially for immunocompromised patients.

Infection and rejection are the most complicated thing to manage in KT recipients. Each of the antithetical complications could arise alone, but sometimes they happen simultaneously. Indeed, the second case had not only various histories of infectious diseases such as cytomegalovirus and herpes zoster virus, but also

acute AMR. Moreover, he had been treated for herpes zoster virus reactivation during the asymptomatic period with supportive care. At the same time, he still had a donor-specific antibody with a high melt flow index (15,108) in HLA-DR. Similarly, the first case also had a history of acute AMR. There was no specific sign of rejection, but considering the risk, we maintained two major immunosuppressants.

Interestingly, both cases showed not only kidney function deterioration but also proteinuria. Previous coronavirus infections, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) developed acute kidney injury in 5% to 15% cases and showed high mortality rate (9, 10). On the contrary, COVID-19 was associated with a high incidence of proteinuria. A recent report showed that 34% of patients showed albuminuria on admission date (11). Likewise, both cases also showed significant proteinuria when they admitted to the hospital. In addition, with improving the clinical course, proteinuria was subsided.

Unfortunately, there is no specific treatment guideline for COVID-19. Lopinavir is an agent used during SARS and MERS epidemics. Because COVID-19 shares 79.5% of sequence identity with SARS-coronavirus (12), it has been suggested that treatment strategy could be shared (13). Also, several cases were recovered from COVID-19 after using lopinavir (14-16). However, drug interactions with calcineurin inhibitors should be considered when lopinavir is initiated in KT recipients. Lopinavir can inhibit the metabolism of tacrolimus (17), which is a substrate of CYP3A4, thereby increasing the blood level of tacrolimus (18). Although the dosage of tacrolimus was only 2 mg per day and the trough level was around 5 ng/dL, 2 days after starting the lopinavir/ritonavir, the tacrolimus trough level abruptly increased in the first case. In addition, it took 10 days to normalize the concentration within the acceptable range. This finding was similar to other cases of liver transplantation (19); thus, physicians should consider indispensable and alternative options before starting this agent. Moreover, after the decision to use this agent, tacrolimus should be skipped before or at the time of start of administration, and the trough level should be cautiously monitored.

We demonstrated two distinct KT recipient cases diagnosed with COVID-19. They had different comorbidities and medical histories and showed different clinical manifestations. By early detection with screening strategy, the second case needed more in-hospital days (17 and 18 days before and after admission to our hospital) than the first case (30 days). However, considering the more vulnerable immunologic background, such as a second KT, ABO-incompatible KT, and various histories of viral infections, early diagnosis with assertive screening could lead to favorable clinical courses. It is difficult to suggest the efficacy of the treatment regimen, but lopinavir/ritonavir should be cautiously used in KT recipients with tacrolimus. On the basis of these few cases, it is necessary to provide baseline information of better outcomes by accumulating multiple new experiences.

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### **Disclosure**

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

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**Table 1.** Changes in laboratory findings of both cases

	Case 1				Case 2		
	On admission	D 7	D 18	D29	On admission	D 7	D 17
Complete blood cells							
White blood cell, / $\mu$ L	6,630	13,910	13,840	4,980	3,950	4,680	5,850
Hemoglobin, g/dL	14.5	12.5	11.9	10.6	14.1	15.0	13.1
Platelet, $10^3/\mu$ L	313	371	323	324	111	129	207
Neutrophil, / $\mu$ L (%)	5,417 (81.7)	12,157 (87.4)	10,740 (77.6)	1,668 (33.5)	2,090 (52.9)	2,434 (52.0)	2,469 (42.2)
Lymphocyte, / $\mu$ L (%)	643 (9.7)	654 (4.7)	1,882 (13.6)	2,092 (42.0)	1,339 (33.9)	1,470 (31.4)	2,469 (42.2)
Monocyte, / $\mu$ L (%)	557 (8.4)	1,085 (7.8)	1,024 (7.4)	891 (17.9)	521 (13.2)	679 (14.5)	801 (13.7)
Sodium, mEq/L	130	134	143	143	133	133	137
Potassium, mEq/L	5.0	4.3	4.3	4.9	4.9	5.2	4.4
BUN, mg/dL	26	23	33	21	33	47	34
Creatinine, mg/dL	2.02	1.59	1.39	1.39	1.85	2.27	1.74
eGFR, mL/min/1.73 m <sup>2</sup>	41.2	55.0	64.7	64.7	39.8	31.1	42.9
Albumin, g/dL	4.2	3.3	3.4	3.8	3.7	3.7	3.7
AST, U/L	32	12	16	20	14	16	15
ALT, U/L	35	21	30	45	10	9	11
CRP, mg/dL	4.6	3.4	0.6	0.1	2.7	2.5	0.1
Urine albumin	2+	1+	negative	trace	2+	1+	trace
uPCR, g/g Cr	1.25	0.87	0.21	0.09	ND	0.75	0.58

## COVID-19

Nasopharyngeal swab	positive	positive	positive	negative	positive	positive	negative
Sputum	positive	positive	positive	negative	positive	positive	negative

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CRP, C-reactive protein; uPCR, urine protein to creatinine ratio; D, admission date; ND, not done

## Figure Legends

### Figure 1. Changes in the clinical parameters, laboratory results, and drug administrations

In the table figure, the blue colored boxes show the use of immunosuppressants with dosages. The red-colored boxes show the antiviral agents used in each day. The gray-colored boxes show a skipped day for immunosuppressants.

In the line plot, the left-sided vertical axis represents body temperature and tacrolimus trough level in top and bottom plots, respectively. The right-sided vertical axis represents the estimated glomerular filtration rate (eGFR) and C-reactive protein (CRP) level in the top and bottom plots, respectively. The horizontal axis represents the days at hospital, in common. The admission date is represented as hospital day 1. The latest day before admission was demonstrated by -26 and -27 in Case 1 and Case 2, respectively.

Case 1 is shown in the (A) plot, and case 2 in the (B) plot.

Abbreviation: MMF, mycophenolate mofetil; PDN, prednisolone; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein

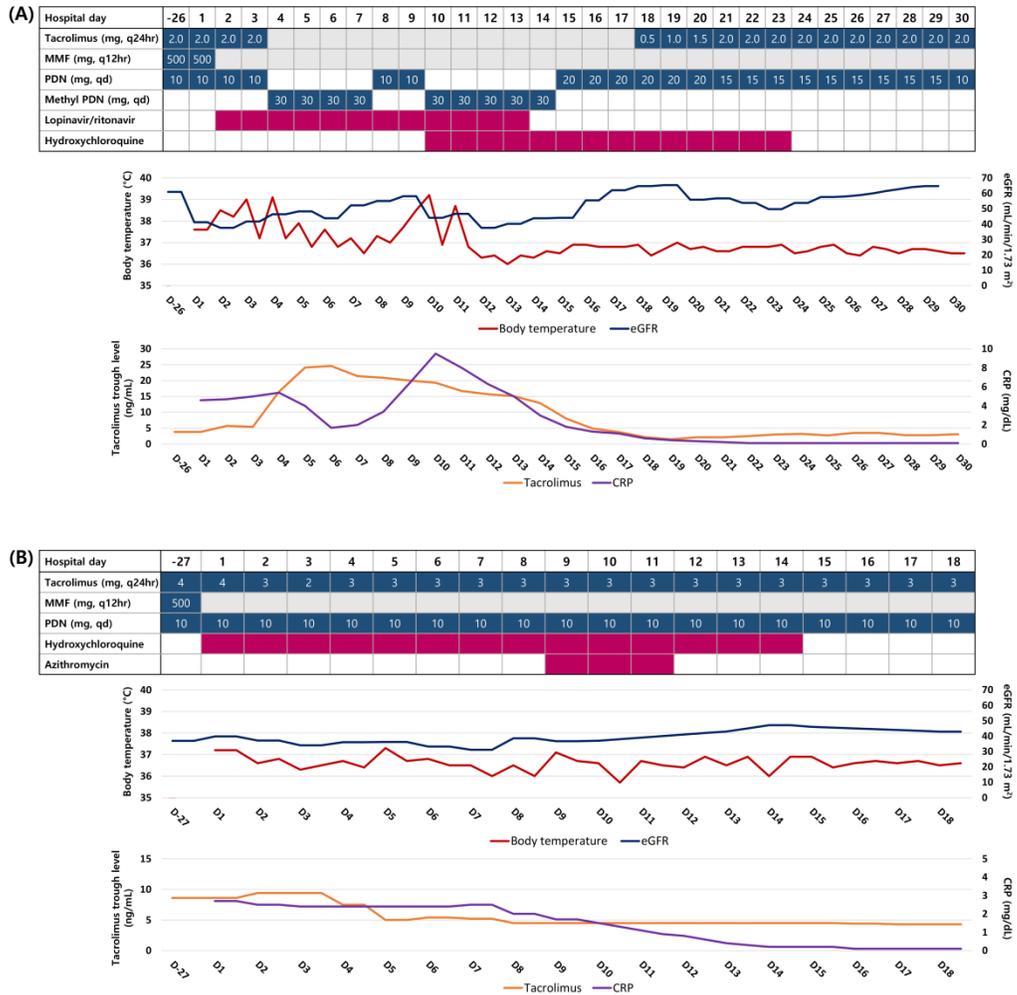
### Figure 2. Changes in chest radiograph findings in Case 1.

The admission date was represented as day 1 (D1). The infiltrative lesion was aggravated on D5. It was started to improve from D14 and further improved on D28.

### Figure 3. Changes in the findings of chest X-ray and chest computed tomography in Case 2.

The first row shows chest computed tomography (CT) findings 1 day before admission, and the second row shows chest CT in hospital day (D) 7. The same columns between the first and second rows show the same plane in the CT. The infiltrative lesion in both lower lung field in the chest CT was more aggravated on D7 than on D1.

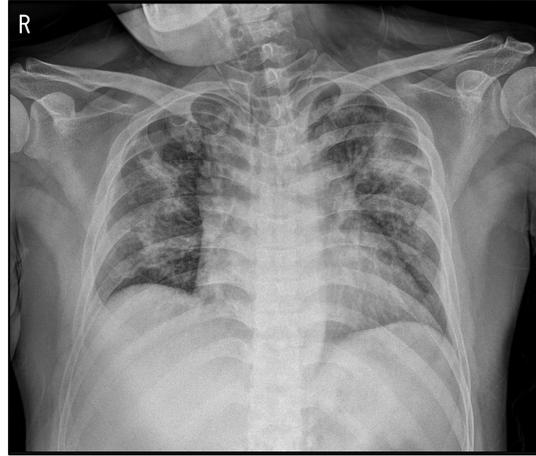
The last row shows the changes in the findings of chest X-ray from admission day to hospital day 18. The infiltrative lesion was aggravated in the image on D7, but it was improved on D18.



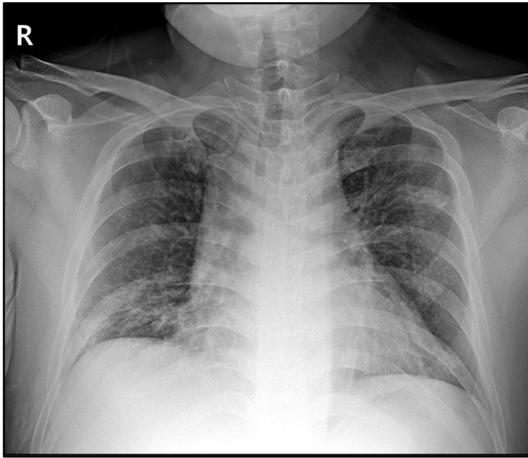
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D1 of admission



D5 of admission

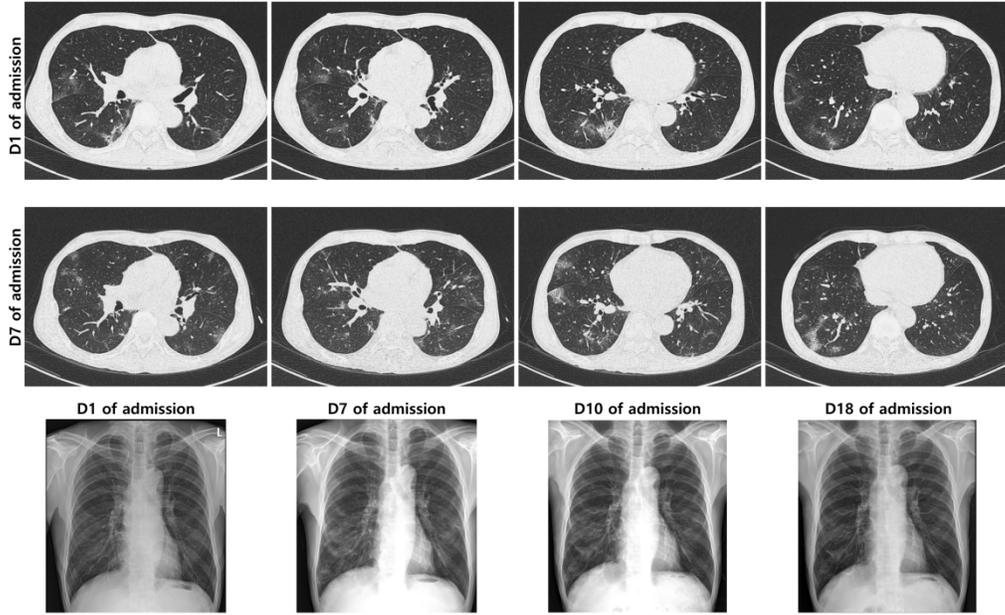


D14 of admission



D28 of admission

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