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Coronavirus Pandemic

Modification of immunosuppressive agents in a kidney transplant recipient with COVID-19 and acute kidney injury

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Abstract

Introduction: An outbreak of coronavirus disease-19 (COVID-19) has occurred in different parts of the world. Although a large piece of information regarding the epidemiology, clinical features, and management of COVID-19 has been reported in the general population, there is very limited data regarding organ transplant recipients, particularly regarding the management of maintenance immunosuppressive agents during infection.

Methodology: We described a case of kidney transplant recipient from Thailand who had COVID-19 pneumonia and severe acute kidney injury.

Results: The patient's serum creatinine peaked at 7.0 mg/dL on day 15 of illness and returned to baseline value of 2.0 mg/dL on day 26 of illness. We have shown how we modified tacrolimus, mycophenolate, and steroids in the patient who had received favipiravir and lopinavir/ritonavir for COVID-19 pneumonia.

Conclusions: In this case, successful modification of this immunosuppressive regimen was accomplished to reduce drug interaction complications, aiming to avoid calcineurin inhibitor nephrotoxicity while maintaining appropriate levels of immunosuppression to prevent organ rejection and to promote the patient's recovery from infection.

Key words: COVID-19; pneumonia; calcineurin inhibitors; drug interaction; immunosuppressive adjustment; immunosuppressive regimen; kidney transplantation.

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Introduction

Coronavirus disease-19 (COVID-19) has become a global pandemic and posted tremendous challenges to the health care system across the globe. Clinical characteristics of COVID-19 have been described in the general population [1–4] and in kidney transplant recipients [5–7]. Clinical presentations of COVID-19 in kidney transplant recipients have been similar to those in the general population in which most of them have a fever (87%) and cough (67%) at the time of presentation [7]. Interestingly, mortality rates in kidney transplant recipients are much higher than that in general population [8]. COVID-19 can lead to kidney allograft dysfunction and multi-organ failure. Whilst common strategy for immunosuppressive management is withdrawal of immunosuppressive agents [5], proper modification of immunosuppressive regimens especially in a situation with resource limitations is still unclear.

In April 2020, a kidney transplant recipient with COVID-19 was admitted to Lampang Hospital, Lampang, Thailand. A written informed consent was obtained from the patient and the study was approved by the ethics committee of Lampang Hospital. Herein, we report an approach for immunosuppressive management in the case of a kidney transplant recipient who developed pneumonia and acute kidney injury from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Case Report

A 39-year-old Thai man who underwent deceased donor kidney transplantation due to end-stage renal disease of unknown etiology 6 years earlier presented

with fever (body temperature of 38.3 ºC), fatigue and dry cough for 3 days. He had no history of allograft rejection with serum creatinine of 2.0 mg/dL at the most recent follow-up visit. He also had chronic viral hepatitis B (HBV) infection which was successfully treated with lamivudine with undetectable HBV viral load. He is now maintained on tacrolimus with a recent trough concentration of 6.8 ng/mL, mycophenolate sodium, prednisolone, enalapril, diltiazem and simvastatin. He had been living with three other family members and one of which had upper respiratory tract symptoms which was finally diagnosed SARS-CoV-2 pneumonia. Due to a history of direct contact, he was identified as patient under investigation and was admitted in the hospital. Nasopharyngeal swab was obtained which revealed negative results for influenza and SARS-CoV-2 on the day of admission. His oxygen saturation was in normal range. Laboratory studies showed lymphopenia and thrombocytopenia (Table 1). His fever and dry cough were still persisted during the first two weeks of hospitalization.

On hospital day 7, patient developed shortness of breath and diarrhea. Chest radiography revealed left lower lung infiltration which progressed to bilateral

Table 1. Symptoms, laboratory results and treatments according to day of illness and hospital day.

	Hospital day													
	D1	**D6**	**D7**	**D9**	**D11**	**D12**	**D13**	**D14**	**D15**	**D17**	**D19**	**D21**	**D23**	**D26**
Day of illness 1	3	8	9	11	13	14	15	16	17	19	21	23	25	28
Dry cough														
Dyspnea														
Diarrhea (times/day)			**3**	**8**	**1**	**4**	**15**	**14**	**6**	**5**	**1**			
Fever (> 37.5 ºC)														
Body temperature (º C)	38.3		38.5	38.3	38.6	39.5	40.2	39.1	37.8	36.5	36.7	36.3	36.6	36.8
FiO_2	RA		RA	RA	RA	NC 3 LPM	HFNC FiO_2 0.6	HFNC FiO_2 0.6	HFNC FiO_2 0.6	HFNC FiO_2 0.4	NC 3 LPM	RA	RA	RA
SpO_2 (%)	97%		96%	98%	96%	95%	98%	98%	100%	100%	100%	97%	98%	98%
Fluid intake (mL)			1,000	2,450	5,200	5,700	2,500	2,000	2,450	3,200	3,300	3,500	3,200	2,950
Urine output (mL)			650	1,650	2,050	2,350	1,100	1,900	2,200	3,200	3,400	3,350	3,100	2,800
Nasopharyngeal swab for SARS-CoV-2 RT-PCR	**Neg**		**Pos**								**Pos**			Neg
Hemoglobin (g/dL)	12.0		11.3	11.2	10.6	11.1		12.6	12.2	12.1	11.3			10.0
White blood cell count (/mm^3)	3,190		2,100	2,100	2,100	6,200		10,000	7,200	3,300	3,300			7,500
Neutrophil (%)	80		65	65	77	88		92	83	69	59			73
Lymphocyte (%)	20		26	24	16	7		2	6	17	24			15
Absolute lymphocyte count (/cu.mm)	638		546	504	336	434		200	432	561	792			1,125
Platelet count (×10^3/mm^3)	80		80	95	101	171		189	205	210	182			191
CRP (mg/L) (normal range, < 10 mg/L)				41.7		96.1		314.3		78.2		17.7		1.9
Ferritin (ng/mL) (normal range, 20 to 250 ng/mL for adult males)				2,790								2,250		
AST (U/L) (normal range, 8 to 48 U/L)	24		91	155	96	78		43	31					42
ALT (U/L)	15		56	101	83	72		47	34					36
BUN (mg/dL)	33		27	33	34	31	34	56	84	95	86	66	40	41
Creatinine (mg/dL)	2.5		2.2	2.8	3.3	3.0	4.0	5.8	7.0	6.3	5.1	3.0	1.7	2.0
Sodium (mmol/L)	133		133	133	132	133	127	131	133	136	136	134	130	131
Potassium (mmol/L)	4.3		4.3	4.9	4.6	4.9	5.6	5.1	4.6	3.7	4.6	4.8	4.6	5.0
Bicarbonate (mmol/L)	29		19	15	15	19	15	15	14	30	30	23	22	23
Therapy														
Azithromycin			**500 mg/day**	**250 mg/day**										
Hydroxychloroquine			**1,200 mg/day**			**800 mg/day**								
Favipiravir			**1,600 mg/day**			**1,400 mg/day**								
Lopinavir/ritonavir						**800/200 mg/day**								
Meropenem						**2 g/day**	**1 g/day**			**500 mg/day**				
Medication dose														
Tacrolimus	**2 mg/day**							**1 mg/day**						
Mycophenolate sodium	**720 mg/day**						CESSATION							**360 mg/day**
Prednisolone	**2.5 mg/day**							**15 mg/day**						**5 mg/day**
Lamivudine				**150 mg/day**						**150 mg/week**				**150 mg/day**
Enalapril	**10 mg/day**						CESSATION							
Diltiazem	**120 mg/day**						CESSATION							
Simvastatin	**40 mg/day**						CESSATION							

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; FiO2: fraction of inspired oxygen; HFNC: high flow nasal cannula; LPM: litter per minute; NC, nasal cannula; RT-PCR: reverse transcriptase polymerase chain reaction, Neg: negative; Pos: positive; RA: room air; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO2: peripheral capillary oxygen saturation. **Bold text** denotes presence of symptoms or treatments.

pulmonary infiltration. Nasopharyngeal swab for SARS-CoV-2 was repeated which returned positive results. Nevertheless, the evaluation for cytomegalovirus and pneumocystis pneumonia was not performed. Treatment with hydroxychloroquine, favipiravir, lopinavir/ritonavir was initiated with good clinical recovery. Immunosuppressive regimen was modified by 50% reduction of tacrolimus, cessation of mycophenolate sodium and increase of prednisolone to prevent adrenal insufficiency (Table 1). Although enalapril was discontinued, his serum creatinine started to increase on hospital day 9 and reached a peak of 7.0 mg/dL on day 15. Tacrolimus trough concentration taken 7 days after starting lopinavir/ritonavir which returned 7 days later was 66.3 ng/mL. The duration of lopinavir/ritonavir treatment was 10 days. At the time we received this result of tacrolimus trough concentration, lopinavir/ritonavir had been discontinued for 4 days. We managed the acute kidney injury by intravenous fluid adjustment and furosemide administration aiming to keep patient in euvolemic state. We did not perform kidney allograft biopsy due to limitations of the hospital facility. With conservative treatments and reduction of immunosuppressive agents, allograft function was continuously improved and serum creatinine returned to baseline levels on hospital day 23. Mycophenolate sodium was resumed at half of the patient's regular dose after repeating the nasopharyngeal swab for SARS-CoV-2 turned to be negative.

The patient symptoms were much improved after hospital day 15. His fever and cough disappeared on hospital day 16. Diarrhea and dyspnea still persisted from hospital day 7 to day 19 and oxygen supplementation could be tapered from a high-flow nasal cannula to nasal cannula on hospital day 19. The patient was dismissed from the hospital after 26 days of admission without any symptoms. Two weeks after discharge from the hospital, the patient reported he was in good clinical conditions and had stable serum creatinine level.

Discussion

International travelers are very important sources of epidemic of SARS-CoV-2 infection in Thailand. The first COVID-19 patient reported in Thailand is a Chinese man traveled from Jinzhou, China [9]. Similarly, international travelers are also important sources of COVID-19 pandemic in Southeast European countries [10]. Here, we have reported one of the first cases of a kidney transplant recipient diagnosed with COVID-19 in Thailand.

The clinical manifestations of COVID-19 in kidney transplant recipients are not different from those in general populations in which fever and cough in accompanied with lymphopenia which are the common features [1–4]. However, mortality rate among kidney transplant recipients is much higher, 28% as compared with 1-5% in patients with COVID-19 in the general population [8]. Recent studies have documented a prevalence of fever, cough, and diarrhea in 58%, 53% and 22% of kidney transplant recipients, respectively [8]. Additionally, lymphocyte count < 1,000 /mm^3, serum ferritin > 900 ng/mL, and acute kidney injury were presented in 79-83%, 17-36% and 30-40% of kidney transplant recipients, respectively [5,6,8]. There were several potential causes of acute kidney injury in our patient including hemodynamic injury from cytokine storm syndrome, alterations of glomerular hemodynamic from enalapril, and tacrolimus-induced nephrotoxicity due to interactions between tacrolimus and ritonavir as ritonavir remarkably reduced tacrolimus metabolism [11]. Modification of immunosuppressive regimen was varied between series, specifically, 71-86% discontinued antimetabolites [7,8], 21% discontinued tacrolimus [8], and some discontinued both [12]. Our approach in this patient was to discontinue mycophenolate sodium and reduced tacrolimus by 50%. With this approach, the patient fully recovered from COVID-19 pneumonia and acute kidney injury.

Our patient had negative results for reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab at the time of presentation. Although the specificity of RT-PCR was high, its sensitivity was still limited, specifically 66-80%. The high false negative rate may be related to low levels of viral ribonucleic acid (RNA) in the early stage of infection [13]. Thus, RT-PCR should be repeated in patients who are highly suspicious for SARS-CoV-2 infection.

There were two learning points from this case. Firstly, although RT-PCR was negative, it should be repeated in patients who are highly susceptible for SARS-CoV-2 infection. Secondly, immunosuppressive agents should be minimized according to the potential for negative drug interactions and severity of acute kidney injury and should be reintroduced if the infections are under control. Further studies are required to determine the best approach to modify an immunosuppressive regimen in kidney transplant recipients with COVID-19 aiming to balance retaining immunity to infection and the prevention of allograft rejection.

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Authors' contribution
Study design: TV, VS, KN; Data acquisition; TV, VS, TS, NC, KL; Data interpretation: TV, VS, KN; Writing of the manuscript: TV, VS, KN; Supervision or mentorship: KN. Each author contributed important intellectual content to the content of this manuscript and all authors approved the final version of the manuscript.

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