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BRIEF COMMUNICATION

NEPHROLOGY WILEY

Case of "relapsing" COVID-19 in a kidney transplant recipient

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Abstract

Clinical outcomes of COVID-19 vary considerably between patients. Little was known about the clinical course and optimal management of immunosuppressed patients infected with SARS-CoV-2. We report a kidney transplant recipient with COVID-19 who presented with pneumonitis and acute kidney injury (AKI). She improved after reduction of immunosuppressive treatment and had two consecutive negative reverse transcription polymerase chain reaction (RT-PCR) tests. Her respiratory tract samples turned positive again afterwards, and she was treated with lopinavir-ritonavir. She had satisfactory virological and clinical response after a prolonged disease course. This case illustrates the risk of relapse or persisting shedding of SARS-CoV-2 in immunosuppressed patients, the important role of viral load monitoring in management, the challenges in balancing the risks of COVID-19 progression and transplant rejection, and the pharmacokinetic interaction between immunosuppressive and antiviral medications.

KEYWORDS

acute kidney injury, COVID-19, kidney transplantation, lopinavir-ritonavir, SARS-CoV-2

As of 28 August 2020, over 24.2 million worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19) pandemic, leading to 827 246 deaths.[1] SARS-CoV-2 is characterized by high infectivity and variable severity. Data in immunocompromised hosts are scarce. We describe a kidney transplant recipient with COVID-19 pneumonitis and AKI, who had a relapsing disease course or prolonged viral shedding, and responded to treatment with lopinavir-ritonavir and continuation of immunosuppressive medications. This case illustrates the atypical course of COVID-19 in immunosuppressed subjects and the importance of viral load monitoring.

MA Becky Mingyao and Hung Ivan Fan Ngai contributed equally to this work.

1 | CASE PRESENTATION

The patient is a 31-year-old woman who underwent deceased donor kidney transplantation in 2016 for kidney failure due to chronic glomerulonephritis. She had been receiving standard triple immunosuppression with pantoprazole and cotrimoxazole prophylaxis for pneumocystitis pneumonia, and antihypertensives including diltiazem and metoprolol. Her serum creatinine (sCr) remained stable at approximately 1.48 mg/dL (eGFR 45 mL/min/1.73 m^2) with no prior episodes of rejection. On 16 February 2020 (day 0), while on-board a cruise-ship in Japan, she had low-grade fever and was mildly dyspneic, and tested positive for SARS-CoV-2 in nasopharyngeal swab and throat swab (NPS/TS) specimens, which were collected in a single aliquot. She was hemodynamically stable and her oxygen saturation was 96% on ambient air. Prednisolone dose (5 mg/D) was unaltered, while the daily dose of tacrolimus (Prograf) was reduced from 2 mg to 1 mg (0.5 mg BD), and mycophenolate mofetil

(Cellcept) from 750 mg to 500 mg (250 mg BD). Fever and dyspnoea subsided on day 4 and C-reactive protein (CRP) also normalized (Table 1). SCr fluctuated between 2.45 and 3.02 mg/dL during hospitalization, and tacrolimus level was 10.5 μg/L on day 10. After two consecutive negative NPS/TS results on day 18, she returned to Hong Kong with the reduced immunosuppression. When she attended scheduled investigations on day 20, she reported new onset of mild myalgia and a low-grade fever (37.8°C) was noted. She did not complain about respiratory symptoms but admitted that she also had new onset of mild dry cough upon direct questioning. Physical findings and oxygenation were normal. She tested positive for SARS-CoV-2 in NPS/TS by real-time reverse transcription polymerase chain reaction (rRT-PCR) (TIB Molbiol, Berlin, Germany), showing a viral load of 196 000 copies/mL. Multiplex PCR tests (BioFire Filmarray, bioMérieux, France) for respiratory viruses were negative. Chest radiograph showed patchy opacities, and high-resolution computed tomography showed bilateral centri-lobular ground-glass abnormalities. White cell count was 4.09×10^9/L, while erythrocyte sedimentation rate was elevated (Table 1). Rectal swab for SARS-CoV-2 was indeterminate on day 21, then became positive. sCr increased to 3.4 mg/dL on day 22, while tacrolimus level was 5.3 μg/L. Urinalysis showed normal findings. The fever and myalgia subsided, but the dry cough persisted. NPS/TS viral load was persistently detected (Figure 1), and lopinavir-ritonavir (400 mg/100 mg bid) was started on day 26. Prograf dose was halved pre-emptively. Tacrolimus level increased to 43 μg/L 2 days later, and Prograf was withheld. She became asymptomatic and CXR cleared after 6 days of anti-viral treatment, and NPS/TS specimens became negative for SARS-CoV-2 3 days later. Serial RT-PCR cycle threshold values were monitored (Table 2). Lopinavir-ritonavir was stopped after 21 days, when the rectal swabs were also negative for SARS-CoV-2. sCr improved to 2.48 mg/dL and tacrolimus level to 6.1 μg/L upon discharge. There were no antibiotics administered. She remained seronegative for IgG antibodies against internal nucleoprotein (anti-NP) and surface spike protein receptor binding domain (anti-RBD). Her latest sCr on 24 April was 1.88 mg/dL.

SUMMARY AT A GLANCE

A kidney transplant recipient with COVID-19, who had a prolonged, apparently relapsing course of SARS-CoV-2 infection is described. This case illustrates the need for vigilance during recovery from COVID-19 in transplant recipients, and some of the challenges with managing immunosuppression and using novel unapproved anti-viral therapies.

2 | DISCUSSION

The clinical course for COVID-19 in renal transplant populations remains to be investigated. Common presentations of patients with COVID-19 include fever, dry cough, dyspnoea, myalgia and diarrhoea. Complications including acute respiratory distress syndrome, cardiac arrhythmias, and acute kidney injury have been reported.[2] Kidney

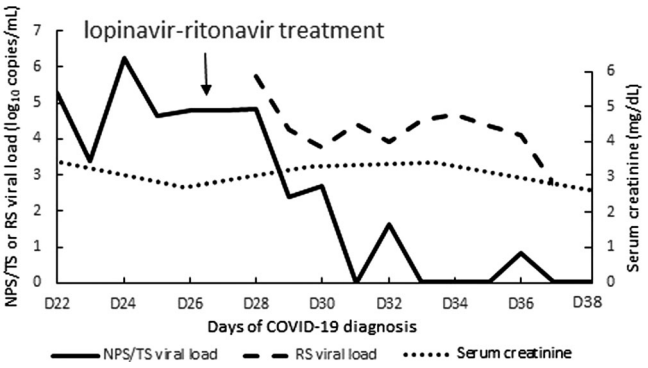

FIGURE 1 Serial profile of SARS-CoV-2 viral load in nasopharyngeal swab/throat swab and rectal swab specimens, and of serum creatinine level, in a kidney transplant recipient

TABLE 1 Serial investigation results in a kidney transplant recipient with COVID-19

Measure	Reference range[a]	Baseline 18 October 2019	Day[b] 3 February 19 2020	Day 9 February 25 2020	Day 15 March 2 2020	Day 22 March 9 2020	Day 26 March 13 20202	Day 29 March 16 2020	Day 33 March 20 2020	Day 37 March 24 2020	Day 41 March 28 2020	Day 45 April 1 2020
WCC ($\times 10^9$/L)	3.89-9.93	9.42	4.92	3.27	5.29	5.34	..	6.59	6.22	5.98	13.5	13.2
Neu ($\times 10^9$/L)	2.01-7.42	4.97	—	—	—	1.69	2	3.38	2.81	3.07	2.57	3
Lym ($\times 10^9$/L)	1.06-3.61	3.5	—	—	—	1.97	..	2.62	2.73	2.24	2.15	2.11
sCr (mg/dL)	0.55-0.93 Jap[c]: 0.39-0.71	1.41	2.11	2.39	2.28	3.41	2.74	3.29	3.42	2.82	2.78	2.39
FK trough[d] (μg/L)	5–10	4.5	—	10.2	6	4.5	8.6	43	48	29	13	17
CRP (mg/dL)	<0.76 Jap: <0.3	0.83	4.01	3.7	2.35	<0.35	<0.35	<0.35	<0.35	0.72	0.71	0.68

Abbreviations: CRP, C-reactive protein; FK, tacrolimus; Jap, Japanese hospital; Lym, lymphocyte count; Neu, neutrophil count; sCr, serum creatinine; WCC, white cell count.

[a]Reference range, the reference range of local laboratory, which is accredited by the College of American Pathologists, is adopted.

[b]Day, the number of days since the first diagnosis of COVID-19.

[c]Jap, the reference range of laboratory at the Japanese hospital.

[d]FK trough, concentration of tacrolimus 12 hours after the last dose.

TABLE 2 Serial RT-PCR cycle threshold values in a kidney transplant recipient with COVID-19

	Day[a] 22	Day 24	Day 26	Day 28	Day 30	Day 32	Day 34	Day36	Day38
Ct value	33.4	33.9	31.8	36.9	37.1	36.3	Undetermined[b]	38.9	Undetermined

Abbreviations: Ct, RT-PCR cycle threshold value.
[a]Day, the number of days since the first diagnosis of COVID-19.
[b]Undetermined, the quantity of viral RNA does not exceed a detection threshold (ie, Ct value >40 cycles).

transplant recipients with COVID-19 can be asymptomatic at presentation.[3] They have less fever as a presenting symptom and a more rapid clinical progression compared with the general population. Up to 50% of transplant recipients may develop AKI during the disease course, as reported in a case series, and the mortality rate can be as high as 28%.[4]

When the patient returned to Hong Kong, we were concerned about the immunosuppressed state of the patient and therefore continued with surveillance testing. Diagnosis of COVID-19 was based on the detection of viral RNA in specimens from upper or lower respiratory tract, which might also be found in stool and urine. It is increasingly recognized that some patients may not have manifestations conforming to previously termed "major clinical signs" including fever or chills, flu-like syndrome, dyspnoea, anosmia, or dysgeusia. The positive NPS/TS result of this patient after two consecutively negative ones in Japan could be a relapse, persistent viral shedding, or reinfection.[5] It was impossible to differentiate retrospectively. The resolution of symptoms with dampening of inflammatory marker CRP correlated with the NPS/TS results in Japan, and new onset of myalgia upon returning to Hong Kong would suggest a relapse. Cytokine storm might account for the recurrence of clinical symptoms, and a drop in cycle threshold (Ct) value resulting in the NPS/TS result reverting to positive after two consecutively negative samples indicated a rebound in viral replication. Radiological changes over time may also aid in the differentiation. On the other hand, a difference in sensitivity of RT-PCR assays might lead to apparent "relapse" of disease. For example, the RT-PCR assay targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel) has been shown to be significantly more sensitive in vitro than other assays, including COVID-19-S, COVID-19-N and RdRp-P2.[6] Unfortunately, we were unable to obtain details of the test kit and viral load data in Japan. Another possibility could be that the NPS/TS results were falsely negative, which could have resulted from improper specimen collection, handling, transport, or presence of amplification inhibitors, or viral load below the detection limit. In this regard, rectal swabs demonstrated a higher positive rate compared with paired respiratory samples, suggesting its role in minimizing false negative rate of diagnosing COVID-19.[7] The possibility of reinfection remained remote as patient did not have any contact history and local prevalence was low at the time (~0.0000139%). Only comparison of viral strains with sequencing could clearly differentiate relapse from reinfection.

Li et al first reported the phenomenon of "turning positive" after two consecutively negative RT-PCR results in 18 out of 610 COVID-19 patients in China.[8] It was postulated that a proportion of "recovered" patients may still be viral carriers. In another cohort of 71 patients with mild-to-moderate COVID-19, the 'turning positive' rate was up to 21.4%.[9] Immunosenescence has been postulated to be a risk factor. There is no data on the 'turning positive' rate in transplant recipients. There is emerging evidence that persistent detection of low viral load by RT-PCR may have little clinical implication as both 'live' and 'dead' viruses are detected. Viral culture, which detects 'replication competent virus' by demonstrating in vitro infectiousness on cell lines, remains the gold standard for detecting clinically significant viral shedding. A high viral load, reflected by the Ct value in quantitative viral RT-PCR, has been associated with isolation of infectious SARS-CoV2 from respiratory tract.[10] A heightened level of caution and increased vigilance with continued surveillance are important in the management of immunosuppressed patients. Whether this be relapse or persistent viral shedding, the prolonged course in this patient was due to her immunocompromised state. The dose of immunosuppressive medications is often reduced or even discontinued when managing kidney transplant recipients with severe infections. However, this may exacerbate the systemic inflammatory response to viral infection in some cases and thus result in more severe clinical manifestations. Also, reducing immunosuppression may also precipitate immune-mediated allograft injury or rejection. Balancing the various risks presents a challenge in clinical management.

Numerous anti-viral medications are under investigation for COVID-19. Lopinavir-ritonavir is a combination of two protease-inhibitors licenced for treating human immunodeficiency virus (HIV) infection. Its use in SARS was associated with a milder disease course, and it inhibits MERS-CoV.[11,12] As the treatment options were very limited, we chosen started the patient on lopinavir-ritonavir based on its efficacy demonstrated against SARS and MERS-CoV. However, it has been fallen out of favour with emerging evidence. Results from a randomized trial in China showed that lopinavir-ritonavir treatment did not shorten the time-to-clinical improvement nor decrease the 28-day mortality rate.[13] However, the trial was underpowered and included a high portion of severely ill patients as shown by the overall mortality rate of 22.1%, compared with 11% to 14.5% in other hospitalized patients.[2] Also, when compared with controls, fewer lopinavir-ritonavir-treated patients developed serious complications including respiratory failure that required invasive mechanical ventilation. Early triple combination of interferon beta-1b, lopinavir-ritonavir and ribavirin has later been shown to be superior than lopinavir-ritonavir alone in alleviating symptoms, shortening the duration of viral shedding and hospital stay in patients with mild-to-moderate COVID-19 in a recent RCT.[14] The data were not yet available at the time of the patient's hospitalization and we have avoided the use of interferon because of its associated risk of rejection. The recent RECOVERY trial demonstrated no beneficial effect of lopinavir-ritonavir compared with supportive care in reducing 28-day mortality in hospitalized COVID-19 patients.[15] A major concern

in organ transplant recipients is the interaction between lopinavir-ritonavir and calcineurin inhibitors, which can raise the plasma levels of both to dangerously high levels, resulting in liver, kidney and immune dysfunctions and prolonged viral shedding.[16] Both tacrolimus and cyclosporine are metabolized by CYP3A enzymes and are subject to transport by *p*-glycoproteins, while protease inhibitors are potent inhibitors of CYP3A4 and inducers of *p*-glycoproteins. The marked increase of tacrolimus in bile and its reabsorption from the gut can result in persistently elevated plasma level despite cessation of dosing, as occurred in the patient.[17] Both tacrolimus and cyclosporine have strong inhibitory effect on the growth of SARS-CoV and HCoV-229E in vitro,[18] suggesting that viral replication is dependent on the immunophilin pathway, but the clinical impact remains to be investigated.

The patient also showed AKI, with subsequent improvement in renal function upon viral clearance. It has been postulated that SARS-CoV-2 enters cells through angiotensin converting enzyme-2 (ACE2), which are highly expressed in the kidneys. In an autopsy study of a COVID-19 patient with oligouric AKI, intracellular viral arrays within proximal tubular epithelial cells were identified by electron microscopy, indicating direct kidney infection.[19] A complex process driven by direct cytopathic effect, cytokine storm, angiotensin II pathway activation, dysregulation of complement, hypercoagulation and microangiopathy together with common risk factors contributes to the development of AKI in COVID-19 patients.[20]

This case illustrates the complexity in managing transplant recipients with COVID-19, highlighting the risk of relapse or persistent viral shedding of SARS-CoV-2 in immunosuppressed patients, the important role of viral load monitoring in clinical management, the challenges in balancing the risk of kidney allograft rejection and the marked pharmacokinetic interactions between immunosuppressive and antiviral medications.

CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

All authors contributed to the clinical management, data collection, data interpretation, literature search and preparation of the manuscript. All authors reviewed and approved the final version of the report.

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