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Acute Kidney Injury Caused by Darunavir in a Patient with COVID-19: A Case Report

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Abstract

Background: A highly contagious virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a pandemic globally. HIV medications were one of the suggested treatments for Coronavirus disease 2019 (COVID-19). Here, we report an unusual adverse drug reaction with darunavir in a SARS-CoV-2-infected patient. **Case Presentation:** This is a case presentation of a 53-year-old male with no past medical history who was diagnosed with COVID-19. One week after initiating treatment, the patient developed acute kidney injury, and his serum creatinine increased significantly. **Conclusion:** As there was no clear justification for renal impairment such as a prerenal or postrenal cause, acute kidney injury, possibly crystal-induced nephropathy, was considered an adverse drug reaction from darunavir.

Keywords

COVID-19, Darunavir, Acute Kidney Injury, SARS-CoV-2

1. Background

In December 2019, a highly contagious virus known as SARS-CoV-2 erupted in Wuhan, China, leading to a viral infection that was named by the World Health Organization (WHO) as COVID-19. By January 2020, the WHO announced it as a pandemic. Globally, more than 50 million people are infected, and more than 1.3 million persons have died since the start of the pandemic. Unfortunately, the number of reported cases and deaths are exponentially increasing [1].

Since there were no antivirals approved by the US Food and Drug Administration (FDA) for managing COVID-19 infection at that time, the use of human

immunodeficiency virus (HIV) protease inhibitors (PIs) was suggested [2]. According to Beck Bo *et al*., darunavir and many other protease inhibitors were predicated to be effective in treating SARS-CoV-2. In this study, a drug-target interaction model was used, and darunavir showed an inhibitory effect on viral proteins of SARS-CoV-2 as it targets viral proteinases. However, its efficacy and safety in treating COVID-19 are still under investigation [3] [4]. The two most common antiviral medications associated with intratubular drug precipitation due to their poor solubility are indinavir and atazanavir. Acute and chronic interstitial nephritis, kidney injury, nephrolithiasis, asymptomatic crystalluria, crystalline nephropathy, and papillary necrosis were reported with these medications. However, darunavir crystals in urine are not commonly seen [5]. Therefore, we describe a case of darunavir-induced acute kidney injury suspecting crystal-induced nephropathy in a patient infected with COVID-19, including his clinical characteristics, treatment used and clinical outcomes.

2. Case Presentation

A 53-year-old male with no past medical history presented to a private clinic with flu-like symptoms. He underwent investigations in a private clinic and was discharged on an antibiotic, anti-pyretic and a cough syrup for 5 days with no improvement. He presented again to the emergency department with a one-week history of fever and intermittent chills. He also had productive cough with thick mucoid sputum. He was tachypneic with mild shortness of breath and complained of myalgia and general malaise. He had no history of recent travel, but he mentioned that his spouse had the same symptoms (**Table 1**).

On admission, he had a temperature of 39˚C with a regular heart rate of 90 bpm and a blood pressure of 128/70 mmHg. His respiratory rate was 28 breaths per minute, and his peripheral oxygen saturation was 94% on room air. Arterial blood gas (ABG) was sent on room air, and a partial oxygen (PO_2) of 62 mmHg (normal 75 to 100 mmHg), PCO_2 of 35 mmHg (normal 35 - 45) mmHg, lactic acid of 0.5 (normal 0.5 - 1 mmol/L), and inflammatory marker were as follows: C reactive protein (CRP) was 50.1 mg/L (normal range 0 - 10 mg/L), and procalcitonin (PCT) was 0.11 ng/mL (minor or no significant inflammatory response: 0.10 - 0.49 ng/mL) (**Table 1**).

All blood electrolytes were within the normal range. The patient's serum creatinine and urea levels were normal on admission, as were his transaminases, bilirubin and albumin. His creatinine clearance was 67 ml/min with no history of renal disease.

Moreover, his chest examination showed normal breath sounds with left side crackles and no wheezes. His chest X-ray image showed multifocal patchy areas of airspace opacities, with the bronchogram noted bilaterally predominantly in the lower zones obscuration of the left costophrenic angle (CP) angle noted (**Figure 1(A)**).

The patient was assessed as having a lower respiratory tract infection, viral in

Table 1. Sociodemographic and clinical characteristics of the patient on admission.

Demographics	
Age (years)	53 years
Gender	Male
Ethnicity	Asian
Clinical features on admission	
Comorbidities	None
Duration of symptoms (Days)	5
Symptoms on admission	cough, fever, intermittent chills, myalgia and general malaise
Temperature	39˚C
Blood pressure	128/70 mmHg
Respiratory rate	28 breaths per minute
Heart rate	90 bpm
O_2 saturation in ambient air	94%
Laboratory results on admission	
White blood cell count	3.8×10^3/uL
Lymphocyte count	0.9×10^3/uL
Platelets count	125×10^3/uL
C-reactive protein	50.1 mg/L
Procalcitonin	0.11 ng/mL
lactic acid	0.5 mmol/L
Severity of the infection at admission	Severe
PO_2	62 mmHg
PCO_2	35 mmHg
Follow up after discharge	7 months

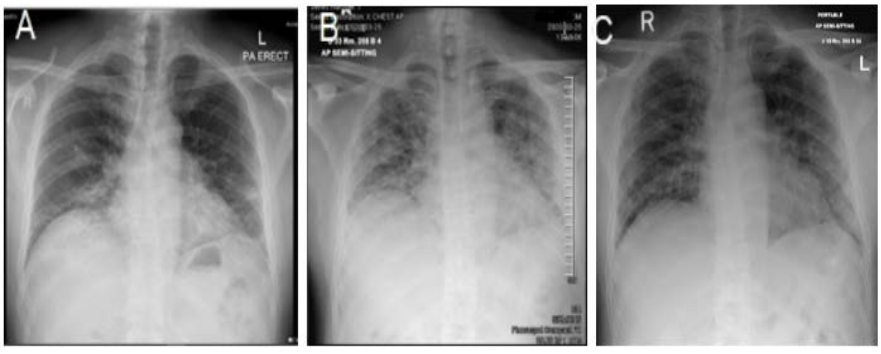

Figure 1. (A)-(C) Chest radiographs. (A), on admission, showing multifocal patchy areas of airspace opacities with the bronchogram noted bilaterally predominantly in the lower zones. (B), on day 4, slight progression of perivascular infiltrates/airspace opacities prominent at the right lung field and left lower lungs. (C), on day 15, Compared with previous study there is no significant interval change noted.

origin. COVID-19 was suspected. Therefore, the patient was kept under airborne and contact isolation. Nasopharyngeal aspirate was sent, and the results were positive for severe respiratory syndrome coronavirus 2. The case was confirmed as COVID-19 pneumonia, and he was admitted to the medical intensive care unit (MICU).

He was started on the treatment suggested by the local protocol for the management of COVID-19, which consists of azithromycin, hydroxychloroquine, cobicistat boosted with darunavir and oseltamivir with concomitant antibiotics (**Figure 2**).

On day 4 of treatment, his fever subsided, and the patient began to improve. He was able to move around with mild tachypnea. The patient was discharged from the MICU to the medical unit, but he still required oxygen on and off through noninvasive ventilation. On day 5 of treatment, chest X-ray was repeated, which showed slight progression of perivascular infiltrates/airspace opacities prominent at the right lung field and left lower lungs (**Figure 1(B)**).

An abrupt rise in the patient's serum creatinine occurred on day 9 of treatment. His serum creatinine increased from 87 μmol/L to 113, 162 and 365 μmol/L on days 9, 10 and 11 of treatment, respectively. He was considered a case of acute kidney injury. His serum creatinine continued to trend until it reached 571 μmol/L. Upon worsening of renal functions, the patient was oliguric and complained of symptoms of nausea and vomiting. He was encouraged to drink water, and intravenous fluid was administered. Oseltamivir and ampicillin-sulbactam were discontinued due to his condition.

Ultrasound for the kidney was performed, and based on the report, the right kidney measured 11.6 × 5.1 cm in length, and the left kidney measured 11 × 5.6 cm. No masses, cysts, calculi, or hydronephrosis were seen. There was a mild bilateral increase in renal cortical echogenicity. The urinary bladder was distended with urine and showed normal wall thickness without masses. The prostate was normal sized (25 cc) with normal echogenicity. Therefore, the impression was a mild bilateral increase in renal parenchymal echogenicity, and there was no sign of obstructive uropathy (**Figure 3**).

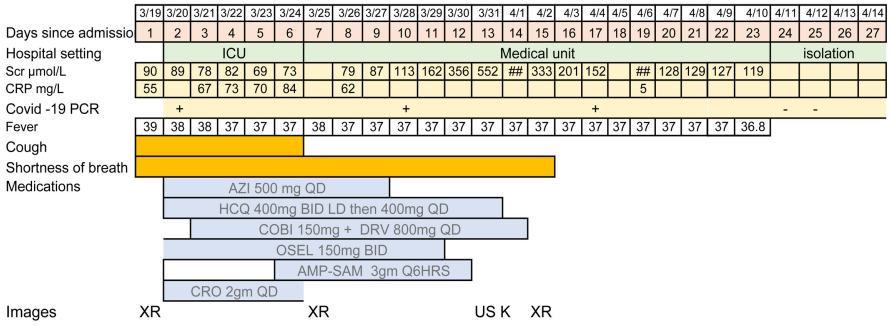

Figure 2. Showing clinical course timeline, Abbreviations: Azithromycin-AZI, Hydroxychloroquine-HCQ, Darunavir-cobicistat-DRV-COBI, Oseltamivir-OSEL, Ampicillin-sulbactam-AMP-SAM, Ceftriaxone-CRO, Chest X-ray-XR, Ultrasound kidney-US K), +: Positive, –: Negative, CRP: C-reactive protein.

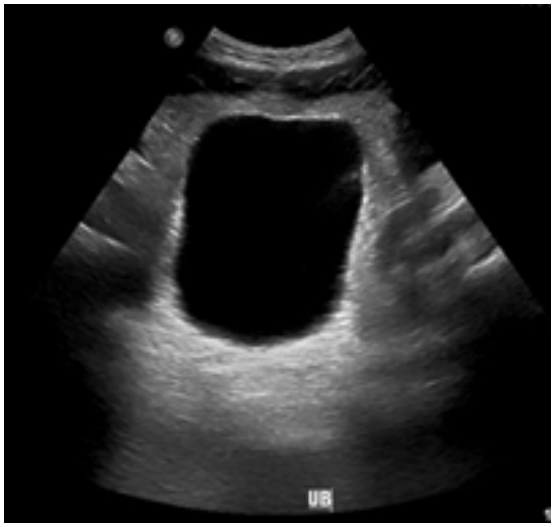

Figure 3. Ultrasound kidney: the right kidney measured 11.6 × 5.1 cm in length, and the left kidney measured 11 × 5.6 cm. No masses, cysts, calculi, or hydronephrosis were seen. There was a mild bilateral increase in renal cortical echogenicity.

At the time of rise in serum creatinine, the urine protein creatinine ratio was 76.00 mg/mmol (normal range <15 mg/mmol), urine eosinophils were negative, creatine kinase came 160 U/L, myoglobin was 193 ng/mL, urine sodium was 32 mmol/L and fractional excretion of sodium (FENa) was 1.9%, indicating the cause of intrinsic acute kidney injury (AKI).

The next day, after stopping darunavir on day 10, the patient's symptoms were settling, and a repeated serum creatinine level had come down to 333 μmol/L, fluid intake 4.3 L and urine output 4.2 L, patient acute kidney injury recovered and decreased gradually to reach 119 μmol/L. He completed his COVID-19 treatment without further problems and had good clinical improvement. On day 15, a chest X-ray was repeated with no significant changes noted (**Figure 1(C)**). Then, he was transferred to the isolation point to complete a total of 28 days from the first positive PCR result. Virologic clearance was reached after 22 days of treatment. The patient was followed up after discharge from quarantine facility with complete resolution of his renal function and there were no other complications.

3. Discussion

DRV (darunavir) is a protease inhibitor approved for the treatment of HIV-1. It was suggested to be effective in treating SARS-CoV-2 and was found to be effective in inhibiting SARS-CoV-2 *in vitro* when used in high concentrations [6]. According to our knowledge, case reports about its adverse drug reaction in COVID patients are not reported, and its safety in COVID is not yet established.

According to Roe J *et al*., 14% of AKI cases in HIV patients were considered as

an adverse drug reaction caused by antiviral therapy [7]. Antiretroviral therapy (ART) has been found to contribute to the development of kidney injury based on many observational studies. PIs such as atazanavir have been associated with the development of renal stones and kidney injury, while tenofovir disoproxil fumarate (TDF), atazanavir (ATV) and lopinavir (LPV) have been associated with acute tubular injury, kidney stone formation and interstitial nephritis [8]. DRV appears to be best tolerated among other ARTs. Jose, S. *et al*. published a cohort study that examined the glomerular filtration rate (GFR) in patients who switched from ATV or LPV to DRV and reported improved renal safety profiles [9]. Moreover, Gao X *et al*. demonstrated that darunavir has a protective effect against HIV-induced renal injury by reducing albuminuria and kidney injury and suppressing HIV-induced upregulation of immune response genes in human kidney cells [10]. Based on a cross-sectional study published by de Lastours *et al*. in 2013, 4 out of 51 HIV patients who received a DRV-based regimen developed high levels of DRV crystals in urine, and the author concluded that DRV potential renal toxicity should be considered [11].

Risk factors that can increase the risk of developing AKI in patients on ART therapy include diabetes mellitus, hypertension, nephrotoxic drug intake, preexisting kidney disease, older age, elevated baseline creatinine level, female gender and African American ethnicity [12] [13]. However, our patient did not have any of the above risk factors, but his acute kidney injury settled after stopping darunavir. Although COVID-19 may present with AKI and other drugs were administered with darunavir we think it is possibly associated with darunavir.

4. Conclusion

We report a clinical course of a healthy male with COVID-19 who developed AKI that we associated with DRV use, recommending prompt identification of DRV nephrotoxicity to moderate the degree of injury, immediate discontinuation of a drug and further testing, such as kidney biopsy, if possible.

Ethics Approval and Consent to Participate

The report was approved by the Institutional Review Board (MRC0420373). Written informed consent was obtained.

Consent of Publication

All coauthors have approved the manuscript and agreed with the publication.

Written informed consent to publish the information in this case report was obtained from the study participant.

Availability of Data and Materials

The clinical data of the case are stored in the hospital electronic medical records and cannot be shared.

Author Contribution

SA: Conceptualization, data curation and original draft preparation. LE: data curation, manuscript review and editing. FR: manuscript review and editing. MO: conceptualization, supervision, manuscript review and editing.

All authors have read and approved the manuscript.

Conflicts of Interest

The authors do not have competing interest in relation to this paper.

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List of Abbreviations

Human immunodeficiency virus (HIV), protease inhibitors (PIs), arterial blood gas (ABG), partial oxygen (PO_2), C reactive protein (CRP), procalcitonin (PCT), costophrenic angles (CP), fractional excretion of sodium (FENa), acute kidney injury (AKI), antiretroviral therapy (ART), tenofovir disoproxil fumarate (TDF), atazanavir (ATV), lopinavir (LPV), glomerular filtration rate (GFR).