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CASE REPORT

Artificial Heart (Clinical)

COVID-19 ARDS in two patients with left ventricular assist device

Mustafa Mert Özgür[1] · Hakan Hançer[1] · Özge Altaş[1] · Kaan Kırali[1]

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Abstract
Coronavirus disease 2019 affected millions of people and caused pneumonia, acute respiratory distress syndrome and increased mortality worldwide. Data from multicenter studies showed that concomitant chronic diseases are associated with severe coronavirus disease. Patients with left ventricular assist device (LVAD) support may also be vulnerable to the disease. Some symptoms of COVID-19 infection like dyspnea and fatigue can overlap with heart failure or LVAD dysfunction. Careful evaluation should be made to diagnose and treat these patients. In these two cases with COVID-19, here we presented the first two patients supported with LVAD in Turkey.

Keywords COVID-19 · LVAD · Left ventricular assist device · Coronavirus

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious and highly contagious disease caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2) that has affected millions of people worldwide [1]. As of October 2020, it has affected approximately more than 40 million people around the world and caused the loss of more than 1 million lives. A specific drug that is effective against COVID-19 is not yet available. It is not yet known whether SARS-CoV-2 results in persistent immunity in patients who were infected and recovered. According to the data obtained worldwide, advanced age (> 60 years), chronic diseases (coronary artery diseases, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney diseases, cancer, etc.), obesity and tobacco use constitute the high-risk group. Global mortality is not more than 3%; however, this rate can rise above 10% in the presence of previously known cardiovascular system diseases [2]. In Turkey, the number of confirmed cases as of December 14, 2020 is 1,836,728 and the number of confirmed deaths is 16,417 (0.8%).

COVID-19 may cause cardiac diseases, such as myocarditis and related heart failure (HF), arrhythmias, venous and/or pulmonary thromboembolism, coronary ischemic heart attacks, as well as worsen pre-existing diseases. It can also aggravate existing chronic HF in patients, who have not yet received any radical HF therapy, i.e., left ventricular assist device (LVAD) support. The known mechanisms driving this situation include a cytokine storm due to the sudden release of pro-inflammatory cytokines, coagulation abnormalities due to destruction of erythrocytes and thrombocytes, increased metabolic demand, and volume overload due to kidney failure can be observed in 15–29% of COVID-19 patients [3].

In this case report, we present two patients with end-stage HF, supported with LVAD, who infected with COVID-19. To our best knowledge, these patients are the first reported LVAD-supported patients affected by COVID-19 in Turkey.

Case 1

In September 2020, a 43-year-old male patient with end-stage HF was admitted to our emergency department 14 months after an LVAD implantation (Heartmate-2 Abbott, Thoratec, Pleasanton, CA) with complaints of dyspnea, fatigue, and numbness in the body. Bilateral pretibial edema was observed on the physical examination, but he was hemodynamically stable, his pulse oxygen saturation

✉ Mustafa Mert Özgür
drmertozgur@gmail.com

[1] Department of Cardiovascular Surgery, Koşuyolu High Specialization Education and Research Hospital, Istanbul, Turkey

(S_pO_2) was 95% in the room air with the normal respiratory rate (18 per minute) and he had a normal body temperature (36.5 °C). He was hospitalized for whole blood tests, COVID-19 Polymerase Chain Reaction (PCR) swab, transthoracic echocardiographic (TTE) examination and also for the thoracic computed tomography (CT). Laboratory tests were around normal, the leukocyte count was 8.8×10^3/μL, (reference value 4.3–10.3×10^3/μL) and D-dimer value (1.42 μg/mL FEU; reference value < 0.55 μg/mL FEU) and C-reactive protein (CRP) values were elevated (55 mg/L; reference value < 3.4 mg/L). Ferritin level (44 ng/mL; reference value 11.4–464 μg/mL) and liver function tests were within the normal range. Biochemical blood tests showed a mild renal insufficiency (creatinine 1.32 mg/dL; reference range 0.7–1.2 mg/dL) and with an elevated international normalized ratio (INR) due to warfarin use (2.3). The level of interleukin-6 was also elevated (36 pg/mL; reference range 1.5–7 pg/mL).

The TTE assessment at the admission showed similar results to the previous routine TTE control two weeks ago with no signs of pump-induced left ventricular suction and a tolerable tricuspid annular plane systolic excursion (TAPSE) at 12 mm. The aorta was opening every two cycles and the interventricular septum was in the midline. There was no deterioration of the cardiac functions on the repeated echocardiographs during his hospitalization. The thoracic CT was evaluated at the admission and there was no sign for a suspected COVID-19 infection. However, when we repeated the thoracic CT at day 4, we observed bilateral sub-pleural and peripheral hazy, mild ground-glass opacities which were evaluated as signs for COVID-19. COVID-19 PCR tests were positive which were done on the day of admission and third day after the admission, respectively.

The antiviral treatment for COVID-19 included favipiravir. Except a sub-febrile body temperature (37 °C) on the fourth day of his admission, which was treated with paracetamol, he had never developed a fever during hospitalization. At the same period, he had an attack of mild dyspnea and decreased S_pO_2 (< 90%) in the room air and treated with a supplemental oxygen (O_2) at 2 L/min through the nasal cannula. After his vital symptoms remained stable and his complaints completely regressed, he was discharged from the hospital on the seventh day. The last COVID-19 PCR test before discharge was negative and he was instructed to stay in the isolation precautions at home. Follow-up was done through phone calls.

Case 2

In October 2020, a 51-year-old male patient with a history of an LVAD implantation (HeartWare®, Medtronic, MN, USA) was admitted a state hospital, with the complaint of fever (38 °C). Since the patient was on the LVAD support he was referred to our hospital for further evaluations. While the chest X-ray showed no findings consistent with COVID-19 infection (Fig. 1A), his CT scan showed peripheral hazy opacities, which was consistent with COVID-19 infection. The patient was hospitalized for further tests. His PCR swab and routine blood tests were taken. Leukocyte count was normal (5.6×10^3/μL; reference range 4.3–10.3×10^3/μL). D-dimer (0.77 μg/mL FEU; reference value 0.55 μg/mL FEU) and CRP (55 mg/L; reference value < 3.4 mg/L) values were elevated. Liver function and renal function tests were within the normal range. He was hemodynamically stable, his S_pO_2 was 97% in the room air with the normal respiratory rate (17 per minute) and he had a normal body temperature (36.6 °C). He was discharged with oral favipiravir treatment (5 day cure) and instructions for self-quarantine.

One week after being discharged, the patient was admitted to the emergency unit with dyspnea. His S_pO_2 was 89% and after oxygen support his arterial O_2 saturation was 95.4%, partial arterial oxygen pressure was 78 mmHg and partial carbon-di-oxide pressure was 26.6 mmHg. His respiratory rate was 30 per minute. The mean arterial pressure was 93 mmHg. His physical examination revealed bilaterally diminished breath sounds and mechanical sound of the device on the left side. His chest X-ray showed bilateral opacities consistent with infection (Fig. 1B). His CT scan showed bilateral diffuse ground-glass opacities (Fig. 1C). He was taken into the intensive care unit for further interventions and monitorization. He was supported with the high-flow O_2. His TTE evaluations were similar to the previous one with TAPSE at 19 mm. The aorta was opening every three to four cycles and the interventricular septum was in the midline. Laboratory tests revealed normal white blood cell count (5.2×10^3/μL; reference range 4.3–10.2×10^3/μL) with mild lymphopenia (0.4×10^3/μL; reference range 0.6–4.1×10^3/μL), and elevated INR (2.3). Levels of lactate dehydrogenase (876 U/L reference range 0–248 U/L), D-dimer (2.48 μg/mL FEU; reference value < 0.55 μg/mL FEU), and CRP (127 mg/L; reference value < 3.4 mg/L), were also elevated. Laboratory parameters during the follow-up are shown in Table 1.

We started the second dose of favipiravir, supplemented with plaquenil and steroid treatment. His clinical condition improved, his dyspnea relieved and need for supplemental O_2 treatment reduced in the next two days. Then, the patient was transferred to the inpatient clinic with 2 L/min O_2 support with arterial O_2 saturation 98%. During the follow-up in the inpatient clinic, his dyspnea decreased and nasal O_2 support was ended. Interleukin-6 (Fig. 2A), D-dimer (Fig. 2B), ferritin and CRP values were decreased. COVID-19 PCR tests for this patient were performed four times: on the day of admission, 3rd and 7th and 14th day after admission. First three tests were positive, but the last was negative. Opacities

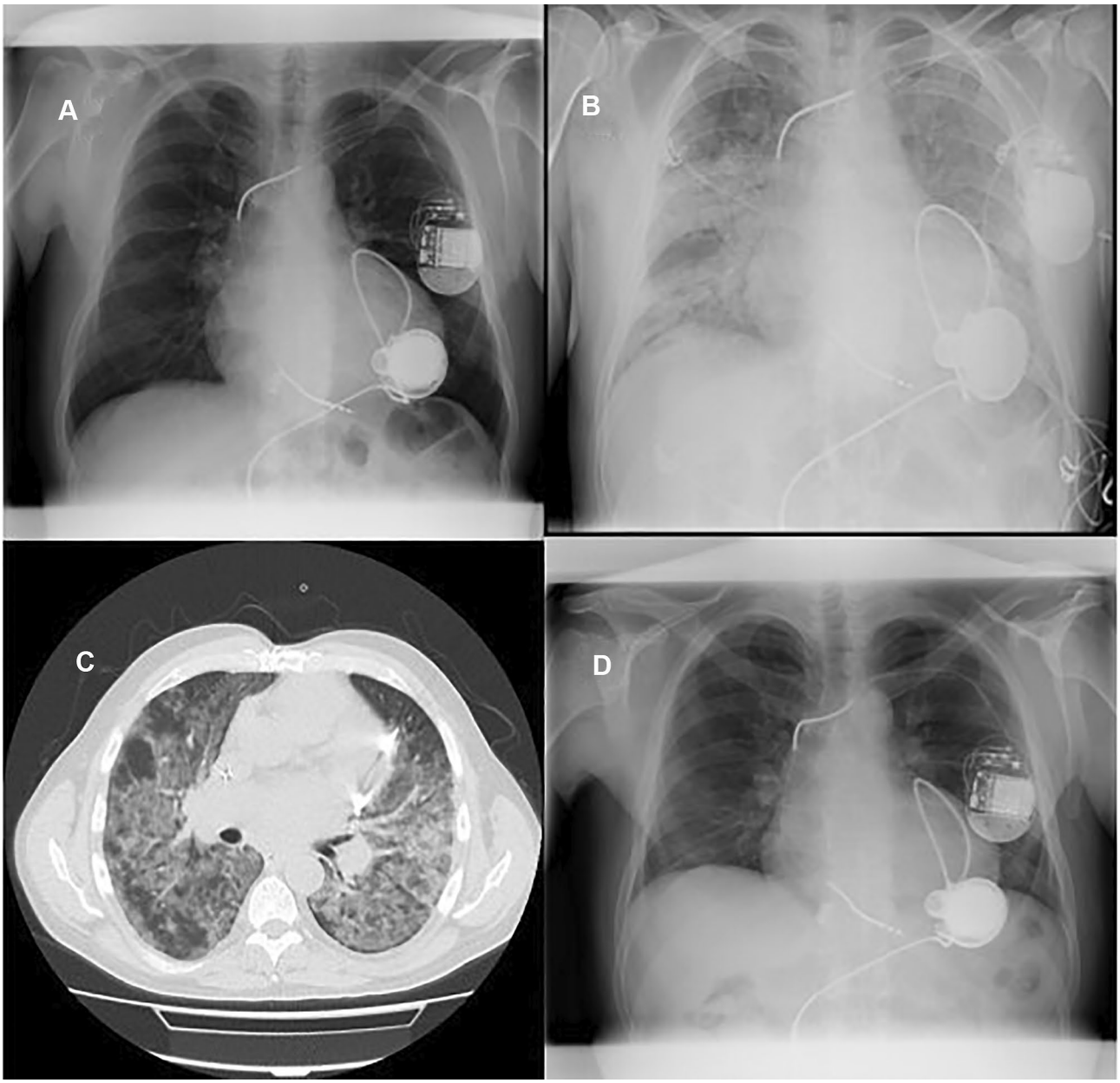

Fig. 1 **A** Chest X-ray of case 2 at the admission with no clear finding of COVID-19 infection. **B**: Chest X-ray of case 2 at 7th day of the admission showing bilateral opacities. **C** Thorax-CT scan of the case 2 at the 7th day of admission showing bilateral diffuse ground-glass opacities. **D** Chest X-ray of case 2 at 14th day of the admission showing diminished opacities

in the chest X-ray diminished (Fig. 1D). He was discharged at the 14th day.

Discussion

The clinical findings of COVID-19 infection can range from asymptomatic disease or mild upper respiratory tract infection to severe viral pneumonia accompanied by respiratory failure or multi-organ dysfunction syndrome. As of today, there are no universally accepted or proven medications or treatment approaches for COVID-19 infections. Studies showed that patients who are older and have cardiovascular comorbidities have a higher risk of mortality with COVID-19 infection [4, 5]. We also know that COVID-19 infection can cause thrombotic events by the activation of coagulation factors [6–8]. LVAD patients are also at high risk of thromboembolic events, such as stroke and pump thrombosis, which may require aggressive antithrombotic therapy.

Table 1 Labaratory parameters of the Case 2

	First admission	Second admission	After ICU	Visit at ward	Before discharge	Control (2 weeks after discharge)
WBC ref: 4.3–10.3 10^3/μL	5.6	5.2	6.5	15.4	15	4
HGB ref: 11.1–16.1 g/dl	11.5	10.3	9.5	9.6	10.4	10.2
HCT ref: % 33–54	35.1	31.1	28.9	81.9	31	30.5
PLT ref: 140–440 10^3/μL	144	171	408	438	357	213
LYM ref: 0.6–4.1 10^3/μL	0.4	0.4	0.5	0.6	1.2	0.9
INR ref: 0.8–1.2	2.4	2.3	3.74	2.37	2.9	1.66
Ferritin ref: 11.4–464 μg/mL	97.80	> 1500.0	> 1500.0	1016	653	–
CRP ref: < 3.4 mg/L	55.5	127	74	100	9.9	3.5

Patients with LVAD support should also be considered as a vulnerable patient population because of the presence of multiple comorbidities and high inflammatory profile. In contrast, decompensated heart failure and low cardiac output state could make the patients more vulnerable to the infection and make it difficult to fight the infection. Although LVAD itself may play a pro-inflammatory role, by increasing cardiac output and improving clinical condition, it could reduce the inflammatory profile especially in contrast to pre-implant condition [9]. Our routine anticoagulation and anti-aggregant therapy after LVAD implantation include 300 mg acetylsalicylic acid per day, 75 mg clopidogrel per day, and warfarin with the target INR level around 2.0.

In our clinic, diagnoses are confirmed by COVID-19 PCR test and swabs are routinely were taken from nasopharyngeal sites of the patients. Favipravir treatment is a routine treatment strategy for COVID-19 infection in our hospital. We sometimes add hydroxyqloroqine to the treatment according to clinical course of the patients. During the management of these two cases in their admission, these routine protocols were continued.

The treatment of LVAD patients with COVID-19 infections may lead to several complications since they do not have standard hemodynamics or systemic circulation. The treatment of these patients should be done in highly specialized centers. LVAD patients with the suspicion of COVID-19 infection should be transferred to a specialized center, while the PCR tests results are pending, to better diagnose and treat LVAD dysfunction, lung edema, right ventricular dysfunction, and to receive better patient management, as soon as they have been stabilized by the admitting hospitals. Raising awareness of LVAD patients in their post-discharge follow-up, teaching them to admit to hospital in case of the slightest problem against the normal course, and detailed examination of these patients at follow-up in terms of a possible infection are important details in early diagnosis and treatment of LVAD dysfunction or asymptomatic infections. Fever is a common symptom of a COVID-19 infection but it also could be seen in driveline infections for that reason detailed wound examinations and query patient's history is crucial for diagnosis and treatment.

In our cases, both patients had symptoms resembling those of atypical heart failure at the presentation. In the first case, there was confusion as to whether or not the symptoms were due to COVID-19, a slight increase in the volume load, heart failure because of the mild COVID-19 symptoms or the lack of a clear explanation by the patient. Especially since the descriptions of dyspnea made us think that there might be circulatory failure related to LVAD. The most important feature of these patients was that they did not show any sign of RV failure. Additionally, we did not find LVAD-related malfunctions or RV failure echo-cardiographically. Although they did not reveal major respiratory signs, COVID-19 PCR was performed as a routine procedure before hospitalization. The clinical profiles of our patients including WBC, CRP, D-dimer and cytokine levels seemed like the clinical profiles of infected LVAD patients [9–11]. The normal D-dimer values of these patients under triple anticoagulant-treatment according to our clinical protocol indicated that they were under protection against thromboembolic events. Although positive PCR tests allowed early identification of asymptomatic COVID, we observed pathologic changes in CT scan and decreasing in S_pO_2 of both patients over time. Basically, O_2 supportive treatment was sufficient for the improvement of the respiratory distress. The antiviral treatment for COVID infection varies in reported infected LVAD patients and mostly they have favorable outcomes with different agents (Table 2) [8–13]. This situation made us to think that there must be some common features of these patients which would have protective effect of disease progression. This factors can be listed as strong anticoagulation, good clinical condition, better hemodynamics, better pulmonary functions.

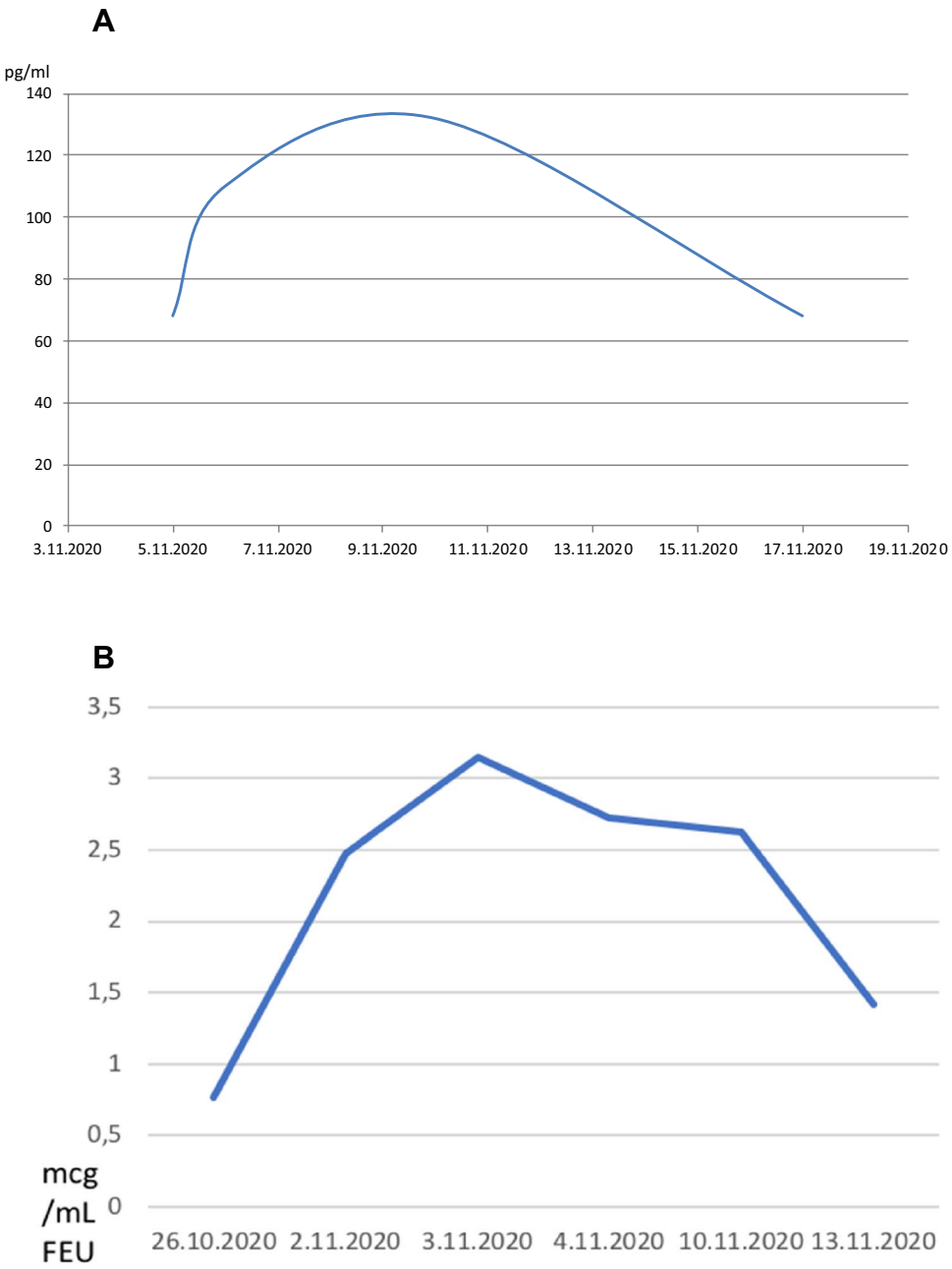

Fig. 2 **A** Course of the interleukin-6 values of case 2. **B** Course of the D-dimer values of case 2

Conclusion

Since patients with LVAD do not have a standard hemodynamics and circulatory physiology, approach and management of these patients may become complicated. Patients with LVAD should monitor closely in line with their complaints. The possibility of COVID-19 infection should be kept in mind and its distinction with heart failure findings should be carefully examined.

Table 2 Literature review for COVID-19 infection and LVAD support

Case report Author	Age Gender of patient	Clinical course	Antiviral medication	Oxygen need	ECMO necessity during hospital admission	Confirmed COVID-19 infection with PCR analysis	Clinical result
Rassaf et al.	30 Male	Patient was admitted with diagnosis of ıdiopathic cardiomyopathy. LVAD was implanted successfully while patient was actively infected with COVID-19	NA	Intubated	Yes	Yes	Discharge
Korada et al	48 Female	She referred to the hospital with respiratory symptoms. Primary evaluation resulted in negative for COVID-19. After discharge and re-admission with same symptoms she was treated for 45-days in hospital for COVID-19	Lopinavir–ritonavir	Nasal oxygen No intubation	No	1. No 2. Yes	Discharge
Singh et al	66 Male	Has ARDS and septic shock. At the time of writing, the patient remains critically ill; however, there has been clinical improvement	First hydroxyqloroqine and oseltamivir Then lopinavir–ritonavir	Intubated	No	Yes	Still in hospital
Frick et al	56 Female	Has a history of pump thrombosis two times. Patient had pump thrombosis at the time of COVID infection again. Treated with heparin	NA	NA	No	Yes	Discharge
Chan et al	70 Male	Had ARDS and MODS	Hydroxyqloroqine then tocilizumab	Intubated	No	Yes	Lost
Kiran et al	54 Male	Previously LVAD implanted patient. The patient has a history of HIV/AIDS infection and Kaposi Sarcoma (treated with radiation.) Had mild COVID-19 symptoms	Hydroxyqloroqine	No need for oxygen	No	Yes	Discharge

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Declarations

Conflict of interest No potential conflict of interest was reported by the authors.

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