Clinical course and challenging management of early COVID-19 infection after heart transplantation: Case report of two patients

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Case Report

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Abstract

Background: There are limited data on Coronavirus disease 2019 (COVID-19) in solid organ transplant patients and especially in heart transplant recipients with only few case reports and case series described so far. Heart transplant recipients may be at particular high risk due to their comorbidities and immunosuppressed state.

Case presentation: This report describes the clinical course and the challenging management of early COVID-19 infection in two heart transplants recipients who were tested positive for the SARS-CoV-2 virus in the perioperative period of the transplant procedure. The two patients developed a severe form of the disease, and ultimately died despite the initiation of an antiviral monotherapy with hydroxychloroquine coupled with the interruption of mycophenolate mofetil.

Conclusions: These two cases illustrate the severity and the poor prognosis of COVID-19 in the perioperative period of a heart transplant. Thorough screening of donors and recipients is mandatory and the issue of asymptomatic carrier need to be addressed.

Background

In the current context of coronavirus disease 2019 (COVID-19), the management of patients with end-stage heart failure on the transplant waiting-list is challenging. To date, only few case reports or small case series of COVID-19 in heart transplant recipients (HTR) have been described in China, Spain, Germany, and the United States, with mainly HTR who were remote from transplant [1–7]. Herein, we report on two HTR who developed and ultimately died from severe COVID-19, a few days after their urgent transplant procedure (TP). Both were completely asymptomatic at their admission in our center with no respiratory complaints. A routine preoperative nasopharyngeal swab (NPS) for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-coV-2) by reverse transcriptase polymerase chain reaction (RT-PCR) assay targeting E and RdRP genes was performed for both patients [8]. The TP were performed the same day and in the same operating room (OR). Test results that were only obtained on postoperative day (POD) 2 were positive for the first recipient and negative for the second. Unfortunately, the second recipient was subsequently tested positive for SARS-CoV-2 at POD2 on a control RT-PCR test performed on that day. These cases highlight the clinical course of these two patients and the difficulties encountered in their management.

Case Presentation

Recipient 1 (Fig.1):

On March 17, 2020, a 59-year-old man with end-stage ischemic heart disease was admitted for heart transplant after being on the waiting list for approximately 12 months. He was obese, and had a history
of mitral annuloplasty surgery 13 years earlier. The last weeks before admission, his clinical condition had worsened with rhythmic instability due to recurrent tachycardia treated by internal electric shocks on several occasions. At home and upon admission, there were no obvious fever or respiratory symptoms. Laboratory findings did not reveal any particular anomaly with a normal hemogram, renal function and C-reactive protein (CRP) (4.4 mg/L, nl: 0-5). The cross match with the donor was negative. Given the COVID-19 pandemic, he was screened for SARS-CoV-2 infection by RT-PCR on NPS. The donor was also screened for SARS-Cov-2 infection and was negative.

The graft was transplanted in the orthotopic position. He was easily weaned off cardiopulmonary bypass (CPB) and transferred to the intensive care unit (ICU) on mild inotropic support. Quickly after his arrival in the ICU, he became hemodynamically unstable despite an adequate filling and required an escalation of the inotropic and vasopressors support. Upon arrival in the OR and after performing a transesophageal echocardiography (TEE), a cardiac tamponade was excluded and it was decided to go for a surgical revision due to a stenosis of the superior vena cava anastomosis. At the end of the intervention, the patient who regained hemodynamic stability was transferred to the ICU.

The induction therapy included a standard triple regimen of decreasing dose of methylprednisolone, a calcineurin inhibitor (tacrolimus) to obtain trough level between 8 to 10 µg/L, and an antimetabolite, mycophenolate mofetil (MM) 1000 mg twice daily. Anti-infectious prophylaxis included sulfamethoxazole 800 mg and trimethoprim 160 mg three times a week and valganciclovir hydrochloride 450 mg once a day.

The results of the preoperative SARS-CoV-2 RT-PCR analysis returned positive on POD 2. Therefore, according to the hospital protocol, the patient received from POD 2 to POD 7, 200 mg of hydroxychloroquine (HCQ) twice daily after a loading dose of 400 mg twice daily.

The immediate postoperative period was marked by the occurrence of right ventricular dysfunction and low cardiac output syndrome requiring further increase in the doses of dobutamine and norepinephrine, as well as the administration of inhaled nitric oxide to overcome refractory hypoxia. He developed an acute renal failure requiring renal replacement therapy. The situation gradually improved until POD14 when the respiratory exchanges started to deteriorate and a chest computed tomography (CT) revealed bilateral ground-glass opacities compatible with a COVID-19 infection (Fig.2). On the same day, a right cardiac catheterization demonstrated mild post-capillary pulmonary hypertension with a slightly reduced cardiac index (Table). The myocardial biopsy did not demonstrate cellular nor humoral rejection. But, analysis by electron microscopy revealed viral-like particles within endothelial cells but not in cardiomyocytes (Fig.3).

Bacterial infection was confirmed by the isolation of Klebsiella oxytoca in bronchoalveolar lavage (BAL) (>10⁶ CFU/ml) and in blood cultures. The patient was treated with cefepime for 10 days. The SARS-coV-2 RT-PCR performed on BAL's fluid revealed high viral load (7.4 log₁₀ copies/mL). At that time MM was withheld and methylprednisolone reduced to 16 mg daily. Unfortunately, the patient’s respiratory
exchanges continued to deteriorate with ineffective prone positioning. Veno-venous extracorporeal membrane oxygenation (ECMO) was not considered in this immunosuppressed patient with more than 14 days of mechanical ventilation. He died on POD 27 of refractory hypoxia, and multiorgan failure. Also, the surgeon tested positive for SARS-CoV-2 on POD 5.

**Recipient 2 (Fig.1):**

The second patient was a 56-year-old woman with decompensated hypertrophic heart disease who had been on the waiting list for more than 12 months. Her past medical history included a surgery for left pulmonary vein stenosis in 2015. She did not have anti-HLA antibodies. At the time of transplant, she was in the cardiology ward on inotropic support for a new episode of heart failure. Indeed, in the past three months, she had been admitted three times for recurrent episode of heart failure treated by Dobutamine. In the ward, she had no fever nor symptoms suggestive of respiratory infections. The biology performed before the heart transplant demonstrated normal white blood cell count (6.15 \(10^3\)/mm\(^3\); nl: 4.6-10.10), a slight anemia (Hg 10 g/dL, nl: 11.7-15), mild renal failure (creatinemia 1.11 mg/dL; nl 0.55-1.02), and inflammatory syndrome (CRP 15.6 mg/L; nl 0-5). The cross match with the donor was negative. She benefitted from systematic SARS-CoV-2 screening by RT-PCR on NPS.

The TP was performed with a donation after circulatory death (DCD) heart procurement procedure as described by our group [9]. The donor was tested negative for SARS-CoV-2. After retrieval, the heart graft was transported to a contiguous OR where the aforementioned TP, as well as the re-exploration just a few hours earlier, were carried out. Usual OR's cleaning, and changing of the whole respiratory circuit as well as the CO\(_2\) sampling line were performed between the two procedures. The graft was transplanted in the orthotopic position. She was easily weaned off CPB and transferred to the ICU.

The induction therapy, and anti-infectious prophylaxis were the same as for the first recipient. The preoperative SARS-CoV-2 RT-PCR performed on NPS was negative. However, given the patient's indirect contact with the first recipient through OR, another NPS was performed on POD 2. The result was reported weakly positive the same day. Therefore, from POD 2 to POD 7, the patient received 200 mg of HCQ twice daily, after a loading dose of 400 mg twice daily.

There were no postoperative complications. Consequently, the patient was discharged from the ICU, and transferred to an isolation ward on POD4. The right heart catheterization assessment was unremarkable (Table) and the myocardial biopsy did not show rejection. As for the first patient, analysis by electron microscopy showed the presence of viral-like elements within endothelial cells, but not in cardiomyocytes (Fig.3).

Her clinical course was uneventful until POD 19 when she became febrile and described breathing difficulties with a gradual decrease of her oxygen saturation requiring oxygen nasal supplementation. The chest CT revealed some ground-glass opacities lesions predominant on the right lung (Fig.2). SARS-CoV-2 RT-PCR performed on BAL fluid tested strongly positive (8log\(_{10}\) copies/mL). Despite any evidence of infection, empirical antibiotic therapy based on azithromycin was initiated for 7 days following
recommendations of the infectious disease team. After progressive worsening of her respiratory status the patient was readmitted to ICU on POD20, where prompt invasive ventilation coupled to prone positioning were required. At that time, MM was withheld. ECMO was not considered in the context of immunosuppression with more than 10 days of mechanical ventilation. Her clinical status continued to decline. Multiresistant *Klebsiella pneumoniae* was identified in bronchial aspirate on POD 34 and was treated with cefepime. She passed away on POD 35 from refractory hypoxemic respiratory failure.

**Discussion And Conclusion**

The global pandemic of COVID-19 has severely challenged the health care systems that face the battle to limit the spread of the SARS-CoV-2 while providing the treatment and care that will save lives. In most countries, cardiac surgery activity has been restricted to urgent or emergent cases, including heart transplantation. The safety of continuing this procedure during the current COVID-19 outbreak is, however, unknown. The literature on this topic is still scanty. HTR appear to be at particular high risk for both acquisition of COVID-19 infection and progression to severe disease due to high rates of comorbidities, immunosuppression, and multiple healthcare contacts [10].

Li et al. were the first to report the clinical course of two HTR with COVID-19. But, the TP were performed respectively 32 and 194 months before the infection [1]. The two patients presented with variable levels of severity, one mild, the other more severe and requiring prolonged hospitalization. Both patients survived the infection. Fernando-Ruiz et al. reported on the occurrence of COVID-19 among 4 HTR in a single center in Spain. The median interval from transplantation was 12.6 years (range, 8.7-17.9 years). One patient died 10 days after admission of respiratory failure, one patient was still in the ICU, while two patients survived and were discharged home [3]. Since these initial reports, other papers describing the clinical course of COVID-19 in HTR have been published from Germany and the United states. They also featured HTR who were remote from transplant and were mostly receiving relatively low-dose maintenance immunosuppression [2,4,5,7]. Recently, Latif et al. described a single-center case series of 28 HTR with confirmed diagnosis of COVID-19 in the United states. The median time from HT was 8.6 years, and the case fatality rate was 25% [6].

To our knowledge, our report is the first to highlight the clinical course of two HTR for whom viral carriage was confirmed by RT-PCR performed on NPS during the perioperative period. Recipient 1 was an unknown asymptomatic carrier before the surgery. It appeared later on, that he lived in an area of high incidence for COVID-19 infection. Recipient 2 had been hospitalized for nine days at time of organ offer. Her preoperative SARS-CoV-2 screening test was negative, but she was further tested positive on POD2.

Defining the precise mechanism of the viral transmission process in our report is challenging. Transmission could theoretically have occurred through inhalation of first recipient’s viral particles aerosolized in the OR. However, given the number of typical air changes per hour and associated reduction in airborne contaminants, the possibility of OR transmission is relatively low [11]. Another possibility is a contamination in the early pre-operative period. The second recipient was never in contact
with the first patient’s surgeon during her stay before transplantation. Among the health care workers (HCW) with exposure to both patients from their hospital admission to their death, only the surgeon of the first procedure was tested positive soon after the intervention. But, at that time, testing was only performed among HCW who exhibited symptoms suggestive of SARS-CoV-2 infection, therefore asymptomatic HCW in close contact with both patients were not tested. Consequently, the origin of the viral transmission was never explained for recipient 2.

Practically, recently updated guidance document from major transplant societies recommend not to perform heart transplantation if the donor or the recipient is screened positive for SARS-CoV-2 [12,13]. However, as illustrated in our cases, the lack of a rapid diagnostic test, the high proportion of asymptomatic carrier [14] capable of transmitting the infection among patient’s acquaintance, the high rate of false negative tests [15], the possibility of donor-recipient transmission, and the absence of massive COVID-19 testing, all currently contribute to the impossibility to timely identify the patients who should not receive an emergency transplant.

The decision to perform two heart TP in the midst of a pandemic with no rapid pre-operative testing available to rule out COVID-19 infection could be seriously questioned. However, at the time of both TP, all Belgian’s transplant centers were still pursuing their program. We were at the beginning of the pandemic in Belgium with 1486 COVID-19 confirmed cases and 14 death in the whole country [16] (Fig.4). There were 500 patients with COVID-19 hospitalized with 100 in the ICU in the whole country. In addition, our hospital’s prevalence of COVID-19 cases was low (28 patients). The two patients were transplanted just before the beginning of the nationwide lockdown (18th march 2020) and there was no indication that they were infected. At that period (17th march 2020), the ISHLT suggested to proceed with transplantation in waitlisted patients as long as there was no recent exposure or symptoms compatible with COVID-19 in the previous 2 weeks. Furthermore, RT-PCR test for SARS-Cov-2 was also recommended depending on timing and testing availability [12]. Despite the fact that the first patient has been called in from home, he had experienced recurrent episodes of life-threatening arrhythmia with a worsening of his clinical status the weeks before his transplant, and the second patient was in the cardiologic ward for a new episode of heart failure requiring inotrop support.

Questions still remain on the optimal management of immunosuppression in transplant recipients with Covid-19. Current guidelines from expert associations, recommend to consider holding MM or azathioprine in case of critical illness [12]. However, whether immunosuppression therapy can modify the course of the disease with either the benefit of a reduced immunological reaction or a greater risk of severe manifestation remains uncertain. In our two asymptomatic patients, we initially continued immunosuppressive drugs without any particular adjustment of the dose while prescribing HCQ known to improve viral clearance. Despite this, the evolution was unfavorable with the appearance of symptoms within 15 days, the standard incubation period for the virus. Even worse, the viral load remained high in both patients despite the interruption of MM in both cases. The two patients finally died. Mortality rates associated with COVID-19 increase sharply with age, and in patients with underlying cardiovascular diseases such as heart failure [17-19].
Endotheliitis may play a major role in the pathophysiology of COVID-19 infection [20], and may explain the association between cardiovascular disease and increased morbidity of this illness. Indeed, we found viral-like particles in the cytoplasm of myocardial's endothelial cells, but not in cardiomyocytes, as it has been described in other organs of patients with COVID-19 [20]. Endotheliitis seems to worsen a preexisting endothelial dysfunction observed in most patients with underlying cardiovascular comorbidities. This result in systemic alteration of the microcirculatory function in different vascular beds causing vasoconstriction, organ ischaemia, inflammation and a pro-coagulant state [20]. It is also likely that the underlying frailty of our patients, related to the heart failure condition may have contributed to their unfavorable outcome.

Therapy for an overt disease is seriously lacking at the moment, although several promising molecules are still under active clinical investigations. Nonetheless, potential interactions between these medications and immunosuppressive drugs, and the choice of the appropriate molecules according to clinical phenotype could add other challenges.

These two cases illustrate very well the severity and the poor prognosis of COVID-19 infection in the immediate aftermath of a heart transplant. As confirmed by several recent clinical trials [21,22], the antiviral monotherapy with HCQ was ineffective in both cases. We did not observe any toxicity of that drug in both patients. The potential benefit of other antiviral and immunomodulator drugs have not been tested.

As transplant clinicians, we must be very careful about continuing the transplant program in this COVID-19 period. After these two cases, our heart transplant program was temporarily suspended. Our transplant policy is now in accordance with updated recommendations of major transplant societies. Donors and recipients are thoroughly screened to exclude infection, and rule out any close contact with a person at risk or diagnosed with COVID-19 in the days preceding the transplant. In addition, after the procedure, patients should be regularly tested for COVID-19.

Declarations

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**Ethics approval:** As a case report, our paper did not require any referral to our institutional clinical ethics committee.

**Conflict of interest:** There is no conflict of interest provide

**Consent to participate:** not applicable

**Competing interest:** The authors declare that they have no competing interests
Consent for publication: Written consent was obtained from both patient's families for publication of both cases, as well as the accompanying images.

Availability of data and materials: The data that supports the findings of this report are available from the corresponding author upon reasonable request.

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List Of Abbreviations

COVID-19: coronavirus disease 2019

CPB: cardiopulmonary bypass

CRP: C reactive protein

CT: computed tomography

DCD: donation after circulatory death

ECMO: extracorporeal membrane oxygenation

HCQ: hydroxychloroquine

HTR: heart transplant recipients

ICU: intensive care unit

ISHLT: The international society for heart and lung transplantation

MM: mycophenolate mofetil

NPS: nasopharyngeal swab

OR: operating room

POD: postoperative day

RT-PCR: reverse transcriptase polymerase chain reaction

SARS-coV-2: severe acute respiratory syndrome coronavirus 2
TEE: transesophageal echocardiography

TP: transplant procedure

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Additional Files

Fig.5-supinfo (.pdf) Evolution of the viral load and the absolute lymphocytes count in recipient 1.

Fig.6-supinfo (.pdf) Evolution of the viral load and the absolute lymphocytes count in recipient 2.

Fig.7-supinfo (.pdf) Laboratory studies of recipient 1 and recipient 2 throughout their clinical course.

Figures
Figure 1

Clinical course of Recipient 1 (A) and Recipient 2 (B). From admission and day of surgery (HTx) to death highlighting the SARS-CoV-2 RNA load (Log10 copies/ml), the ward and ICU length of stay, Diagnostic and therapeutic interventions such as Chest CT, Myocardial Biopsy, BAL, initiation of antibiotics, and HCQ. (A) MM was withheld on POD 16. The Clinical deterioration observed on POD 14 is close to the peak of the viral Load observed on POD 16. (B) MM was withheld on POD 20. We can see that the deterioration...
of the patient’s clinical status on POD 19 coincides with a peak of the viral load. The SARS-CoV-2 RNA load is expressed by log10 copies per milliliters. Two RT-PCR assays were used due to a change on the testing method of the laboratory. The first one is targeting the E and RdRP gene (Corman V.) and the second one is the automated Cobas® SARS-CoV-2 molecular test (Cobas 6800 Roche) targeting E and ORF1ab genes. Only the E gene is illustrated in the figure. ABt, antibiotics; BAL, bronchoalveolar lavage; Chest CT, chest computed tomography; HTx, heart transplantation; HCQ, hydroxychloroquine; ICU, intensive care unit; MM, mycophenolate mofetil; POD, postoperative day; RT-PCR, reverse transcriptase polymerase chain reaction.

Figure 2

Chest X-ray and CT of recipient 1 (A) and recipient 2 (B). (A). Progressive occurrence of pulmonary lesions during the postoperative course. The black arrows illustrate the ground-glass opacities lesions compatible with COVID-19 infection on POD 14. The blue arrows illustrate bilateral parenchymal patchy consolidations at POD 25. (B). Progressive occurrence of pulmonary lesions during the postoperative course until readmission in the intensive care unit on POD 20 where we can clearly see the ground-glass opacities lesions compatible with COVID-19 infection at POD 19 (black arrow), and bilateral patchy consolidations at POD 20 (blue arrow). POD, Postoperative day.
Figure 3

Electron microscopy of heart tissue specimens from recipient 1 (POD14) (A-B) and 2 (POD12) (C-D) A-D. Transmission electron microscopy representative examples demonstrating viral particles (arrows) in the cytoplasm of endothelial cells with one showing an elongated nucleus (asterisk). The morphology associating a dense circular rim and a clear center (arrow) is consistent with coronavirus-like particles. POD, postoperative day Transmission electron microscopy Tissues were fixed at 4°C in 4% glutaraldehyde (Laborimpex, Brussels, Belgium) in phosphate buffer at pH 7.4, postfixed in 1% osmium tetroxide (Laborimpex, Brussels, Belgium) for 1 H at 4 °C. They were then dehydrated in graded (70%, 90%, 100%) ethanol solutions (VWR International, Leuven, Belgium) and propylene oxide (Laborimpex, Brussels, Belgium), embedded in epon (SERVA, Zandhoven, Belgium) and hardened at 60 °C. Semi-thin sections were stained with 0.5% toluidine blue and examined by light microscopy. Ultra-thin sections (80 nm) were stained with uranyl acetate (Fluka, Bornem, Belgium) and lead citrate (Leica, Aartselaar, Belgium). These sections were examined using an EM 910 transmission electron microscope (60 kV) (Zeiss, Belgium).
Figure 4

Total confirmed COVID-19 deaths and cases in Belgium. (https://www.ecdc.europa.eu/en/covid-19-pandemic) The Blue arrow represents the date of the two transplant procedures. The confirmed counts shown here are lower than the total counts. The main reason for this is limited testing and challenges in the attribution of the cause of death (Source: European CDC-Situation update Worldwide-Last updated 29th June, 11)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FIGURE5suppinfo.pdf
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