ABSTRACT

Review of the literature and reported case series has not reported an increased risk of SARS-CoV-2 infection in heart transplant recipients. However, this population is at increased risk of a more severe infection with increased mortality because of age and the presence of multiple comorbid conditions. There is no significant difference in presenting symptoms in transplant recipients as compared to nontransplant patients, although diarrhea has been reported to be more frequent in transplant patients, a common side effect of immunosuppressive medications. Standard preventive measures have been shown to be equally protective in heart transplant recipients. Risk factors for severe disease and mortality are similar in both transplant recipients and nontransplant patients and include older age and the presence of comorbidities. Hypertension being the most common. The SARS-CoV-2 infection did not increase the risk of transplant allograft rejection. Currently, there are no specific treatment recommendations for SARS-CoV-2 infection in transplant recipients. However, the International Society of Heart and Lung and Transplant has issued guidance on how to modulate immunosuppressive therapy during SARS-CoV-2 infection.

Key words: COVID-19, heart transplant, immunosuppressive therapy, SARS-COV-2

CASE PRESENTATION

This is a case of a 72-year-old female patient who was a recipient of orthotopic heart transplantation in 2007 in the USA for nonischemic dilated cardiomyopathy. In 2014, she was found to have cardiac allograft vasculopathy for which she underwent percutaneous revascularization with stenting to the left anterior descending coronary artery. Over the past few years, she has had multiple admissions with decompensated heart failure and preserved left ventricular ejection fraction (LVEF 60%). Approximately 6 months back, after a thorough evaluation in her transplant center in the USA, she was put on continuous ambulatory intravenous (IV) infusion of milrinone for heart failure with low cardiac output.

She also has multiple comorbid conditions with diabetes mellitus, hypertension, chronic kidney disease (Stage 3A), obstructive sleep apnea, and chronic macrocytic anemia requiring frequent blood transfusions, a history of lacunar ischemic stroke in 2017 and recurrent urinary tract infections (for which she was put on nitrofurantoin prophylaxis as per ID team recommendations). Her immunosuppressive therapy included tacrolimus 1 mg twice daily and prednisolone 5 mg daily.

Her other home medications are continuous ambulatory milrinone IV infusion through a portable pump, amlodipine, aspirin, hydralazine, furosemide, ivabradine, digoxin, allopurinol, pantoprazole, pravastatin, and subcutaneous insulin injections.

She was admitted to the hospital on April 1, 2020 with a 2-day history of recurrent vomiting and frequent watery diarrhea. There was no associated abdominal pain. On initial clinical examination, she was dehydrated, had low-grade fever (temp 37.5°C–37.9°C), a regular heart rate at 100 bpm, blood pressure 123/59, relative risk 20/min, and oxygen saturation (SpO2) 99% on room
air. Cardiovascular examination was unremarkable, and her chest was clear on auscultation. Her abdomen was soft, lax with no tenderness, or organomegaly.

She was admitted to the isolation room of the medical ward. During her stay, she continued to have spikes of fever and became increasingly dyspneic with tachypnoic. She had episodes of desaturation (SpO2 90%) requiring intermittent noninvasive ventilatory support with oxygen through continuous positive airway pressure.

Her blood tests are detailed below [Table 1]. Hemoglobin was 6.7 requiring transfusion of 2 units of packed red blood cells. Hyponatremia, thought to be secondary to diarrhea, was corrected by IV replacement. Her chest X-ray on day 3 [Figure 1] showed increased broncho vascular markings and mild left-sided pleural effusion/thickening as compared to her chest X-ray on admission [Figure 2].

Transthoracic echocardiography showed normal cardiac allograft systolic function with an LVEF of 60% and no regional wall motion abnormality. Given her fever, symptoms of worsening dyspnea, chest X-ray findings, and the ongoing COVID-19 pandemic, SARS-CoV-2 nasopharyngeal swab polymerase chain reaction (PCR) was requested and reported as positive. Being a heart transplantation recipient on immunosuppressive therapy, she was transferred to the medical intensive care unit (ICU). In consultation with the infectious disease transplant team, she was treated with azithromycin, hydroxychloroquine, and oseltamivir, as per the standard local hospital guidelines for Covid-19 at the time.

Heart failure team recommended to maintain the same immunosuppressive therapy of tacrolimus 1 mg bid and prednisolone 5 mg daily. Blood cultures and stool cultures were negative. Stool test was negative for *Clostridium difficile* toxin. Urine culture grew extended-spectrum beta-lactamase *Escherichia coli* and *Klebsiella pneumoniae* for which she received ertapenem as per the urine culture sensitivity report. Daily electrocardiograms (ECGs) showed no QT prolongation during her hospital stay.

She gradually improved clinically and became afebrile. SpO2 gradually normalized without the need for supplementary oxygen. She remained vitally stable throughout with her stay. Repeat SARS-CoV-2 PCR was subsequently negative and 1 week later, her repeat urine culture showed no growth. CRP was reduced from 54 to <5 prior to discharge, and she was discharged home on day 12 on April 12, 2020.

**DISCUSSION**

We report a case of COVID-19 occurring in a patient with a history of heart transplantation 13 years back and multiple comorbidities putting her at high risk for severe disease and high mortality. She acquired the infection from the community. Her presenting symptoms were mainly gastrointestinal (GI). She developed respiratory symptoms during her hospital stay and was tested positive for SARS-CoV-2.

COVID-19 infection commonly presents with fever and respiratory tract symptoms but can manifest in different ways including GI symptoms. In transplant patients, diarrhea can also be a result of immunosuppressive therapy (tacrolimus and mycophenolate mofetil). She was treated in ICU with azithromycin, hydroxychloroquine, and oseltamivir for COVID-19 infection. She also received antibiotics (Ertapenem) for a concomitant urinary tract infection. She was monitored for QT prolongation...
with daily ECGs. This is especially important in these complex patients receiving the above medications.

Transsthoracic echocardiography showed normal allograft systolic function without echocardiographic evidence of rejection. Immunosuppressive therapy with tacrolimus and prednisolone was maintained without dose adjustment. The tacrolimus level was monitored and was 5.1 ng/ml, which was appropriate for her.

**Risk and severity of infection**

Currently, there is no evidence to suggest that transplant patients are at higher risk of acquiring COVID-19 infection as per the international society of the heart and lung transplant (ISHLT), but they are at risk of more severe disease because they are older and have comorbidities.[1] The WHO clinical management of COVID-19 guidance document dated May 27, 2020 identified age >60 years (increasing with age), underlying noncommunicable diseases (NCDs) such as diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immunosuppression, cancer, and smoking as risk factors for severe disease.[2]

Chronic immunosuppression in patients with solid organ recipients increases the risk of severe infection. The intensity of immunosuppressive therapy depends on the duration of the transplant. It is typically more intensive in the immediate posttransplant period and gets less subsequently. The more intensive the immunosuppressive therapy, the higher the risk of serious infection.[3]

**Mortality**

A casecontrol study which compared 47 solid organ transplant recipients (38 kidney and 9 nonkidney) to 100 consecutive hospitalized nontransplant COVID-19 patients (control) reported that age >60 years and severity of COVID-19 on presentation strongly correlated with mortality, while transplant status by itself did not increase the risk for mortality.[4]

The presence of multiple comorbidities in the heart transplant patients might explain the high mortality in this population. In a case series of 28 heart transplant patients, it was found that the most common comorbidity was hypertension (71%), followed by diabetes mellitus (61%), chronic kidney disease (36%), and obesity (25%). Cardiac allograft vasculopathy and preexisting allograft dysfunction were present in 57% and 14% of patients, respectively, and the case fatality rate of 25% was observed.[5]

The data from two large series of heart transplant recipients with SARS-CoV-2 infection[5,6] has shown that these patients are elderly and have co-morbidities, which put them at high risk of severe disease and high mortality.

A case series of SARS-CoV-2 infection in 26 heart transplant recipients from Italy showed that of those who died, the median time from heart transplant was 13 years as compared to a median of 5 years in the survivors. An interesting finding was that there were seven patients who received a heart transplant after the COVID-19 outbreak in China and all of them survived. It was also noticed that all patients on steroids survived.[8]

**Clinical manifestations**

Clinical manifestations of SARS-CoV-2 infection in heart transplant patients are similar to that of nontransplant patients.[5-8]

In a meta-analysis by Rodriguez-Morales et al., the most prevalent clinical manifestations of SARS-CoV-2 infection in nontransplant patients were fever (88.7%), cough (57.6%), and dyspnoea (45.6%). Myalgia or fatigue (29.4%), sore throat (11%), headache (8%), and diarrhea (6%) were less frequent. In this study, the mean age of the patients was 51.97 years, and 55.9% of them were male.[9]

In a retrospective review by Latif et al. of 28 heart transplant recipients with SARS-CoV-2 infection from New York, fever was the presenting symptom in 83% of the patients, dyspnea or cough in 91% and GI symptoms in 83% of the cohort. The median age of patients was 64 years, and 79% of them were men, and the median time from transplant was 8.6 years.[9]

Interestingly, diarrhea was more common in transplant patients than nontransplant patients. One of the possible explanations for this could be the side effects of immunosuppressive therapy such as tacrolimus and mycophenolate mofetil.

**Table 1: Laboratory findings on admission**

| Laboratory Findings | Admission | Normal range |
|---------------------|-----------|--------------|
| WBC                 | 7.6       | 4.0-10.0     |
| Lymphocytes         | 1.4 (18%) | 1.0-3.0      |
| Hb (g/dl)           | 8.0-6.7-8.6 | 12.0-15.0   |
| Platelets           | 568       | 150-400      |
| Urea (mmol/L)       | 7.4-6.48  | 2.8-8.1      |
| Creatinine (umol/L) | 129-77    | 44-80        |
| Sodium (mmol/L)     | 120-133   | 136-145      |
| Potassium (mmol/L)  | 5.7-4.8   | 3.5-5.1      |
| Chloride (mmol/L)   | 88-98     | 98-107       |
| ALT (U/L)           | 10        | 0-33         |
| AST (U/L)           | 9         | 0-32         |
| Trop T (ng/L)       | 24        | 3-10         |
| NT pro-BNP (pg/ml)  | 437-1276  | 0-272        |
| CRP                 | 54.4-5.0  | 0-5          |
| LDH (U/L)           | 199       | 135-214      |
| Ferritin (ug/L)     | 1161      | 18-340       |
| Procalcitonin (ng/ml) | 0.13   |              |
| Tacrolimus level (ng/ml) | 5.1    |              |
| Lactic acid         | 1.8       |              |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; WBC: White blood cell; LDH: Lactate dehydrogenase; CRP: C-reactive protein; Hb: Haemoglobin
Rejection
In a review of 28 heart transplant recipients with SARS-CoV-2 infection, none of the patients had symptoms or signs of acute graft rejection and no drop in left ventricular ejection fraction by echocardiographic assessment. Seven of them had a routine endomyocardial biopsy which was negative for rejection.[5]

Another review of 90 solid organ transplant recipients (kidney, lung, liver, and heart) with SARS-CoV-2 infection did not report any cases of rejection.[10]

Treatment
Management of this population is complex and treatment of Covid-19 in this patient population requires careful consideration of disease severity, patient comorbidities, drug availability, pertinent drug-drug interactions, and expected toxicities of the agents (such as tacrolimus and cyclosporine).

According to ISHLT, those with mild disease, home quarantine for 2 weeks is recommended with frequent remote telehealth monitoring to assess for any worsening symptoms. The same doses of immunosuppressive therapy are to be continued. For patients with moderate and severe disease, it is recommended to admit patients for supportive care and to consider holding mycophenolate mofetil or azathioprine with close monitoring for rejection.[1]

Furthermore, blood levels of immunosuppressive therapy have to be monitored as the most commonly used drugs such as azithromycin and hydroxychloroquine are CYP3A4 inhibitors and significantly increase cyclosporine concentrations.[11,12]

Similarly, lopinavir–ritonavir is a strong CYP3A4 inhibitor that can increase both tacrolimus and cyclosporine concentrations.[11,13] Therefore, careful monitoring of tacrolimus and cyclosporine levels is recommended when these drugs are used.

CONCLUSION
Heart transplant recipients with SARS-CoV-2 infections are at high risk of severe disease and mortality because of their older age and multiple comorbidities. There are no specific recommendations on COVID-19 specific treatment at the current time; they should be treated as per local hospital guidelines.

Maintenance of corticosteroids seems to be safe in transplant patients infected with SARS-CoV-2. Attention should be paid to drug-drug interaction, and immunosuppressant drug levels should be closely monitored as some medications such as azithromycin and hydroxychloroquine may increase their blood levels.

Immunosuppressive therapies should be continued except for mycophenolate and azathioprine, which should be stopped, and patients closely monitored for symptoms and signs of allograft rejection. Currently, there is no data to suggest that these patients are at high risk of rejection because of SARS-CoV-2 infection.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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