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COVID-19-related myocarditis post-heart transplantation

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ABSTRACT

This report describes the first heart transplantation recipient with acute biventricular heart failure symptoms caused by a post-myocarditis state, late after a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. No other viral pathogens could be detected. Computed tomography angiography did not show cardiac allograft vasculopathy, and myocardial biopsy demonstrated no clinically relevant rejection. Subsequent cardiovascular magnetic resonance imaging revealed extensive epicardial delayed enhancement without myocardial edema. Heart failure medication was initiated and an implantable cardioverter defibrillator was implanted (due to non-sustained ventricular tachycardias), leading to a partial recovery of the ejection fraction. Further studies are needed to investigate the number of heart transplant recipients with myocardial damage after a SARS-CoV-2 infection.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues, with 122.5 million cases and over 2.7 million deaths reported by the World Health Organization (WHO) on March 23, 2021 (World Health Organisation (WHO, 2021). The virus has a greater impact on immunocompromised patients such as cancer patients (Belsky et al., 2021; Jindal et al., 2020), stem cell transplant patients (Belsky et al., 2021; Sahu et al., 2020), HIV patients (Patel et al., 2021), and solid organ transplant recipients (Belsky et al., 2021), including heart transplant patients (Marcondes-Braga et al., 2021). A case of COVID-19-related post-myocarditis state on magnetic resonance imaging (MRI), occurring late after initial infection in a heart transplant recipient, is reported.

Case report

A 50-year-old patient, six years post-heart transplantation (due to dilated cardiomyopathy), who was scheduled for an annual check-up in March 2020, called the outpatient clinic with complaints of fever (38.5 °C), dyspnea, and malaise. The patient was seen in the emergency room and was admitted with desaturation (92%) and bilateral crepitations in the basal lung fields. Chest computed tomography (CT) demonstrated lung abnormalities with a high suspicion (CO-RADS 5) (Prokop et al., 2020) for a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (severity score 15). A nasopharyngeal swab tested positive for SARS-CoV-2 RNA by real-time polymerase chain reaction (RT-PCR). Mycophenolate mofetil was temporarily stopped and the patient's prednisone dosage was increased, while tacrolimus was continued. Furthermore, the patient received chloroquine: a 600 mg loading dosage and 300 mg 12 h later, followed by 300 mg chloroquine twice daily with a total treatment duration of five days. No intubation was necessary during the admission, however supplemental oxygen was administered (maximum of five liters). The patient was discharged after six days.

In June, the patient had a delayed annual heart transplantation check-up. Blood results demonstrated positive serology for SARS-CoV-2 (Wantai SARS-CoV-2 Ab ELISA and Wantai SARS-CoV-2 IgM ELISA) and a slightly elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) of 113 pmol/l compared to 26 pmol/l the year before. Transthoracic echocardiography demonstrated normal left and right ventricular function, with an E:E′ that increased from 9 to 15 and no valvular abnormalities. Coronary CT

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displayed an Agatston calcium score of 0 and a small eccentric plaque in the proximal left anterior descending artery, without significant stenoses. No persistent abnormalities were seen in the lung.

The patient's mycophenolate mofetil dosage was increased and a follow-up of NT-proBNP was planned. However, within six weeks, the patient presented with acute symptoms of cardiac decompensation with an NT-proBNP of 212 pmol/l, which increased to 519 pmol/l in two days, and a high-sensitivity troponin of 55 ng/l. Transthoracic echocardiography demonstrated biventricular failure and congestion. As rejection was suspected, methylprednisolone 1 g once daily was administered for three consecutive days, as were intravenous diuretics. A biopsy demonstrated focal subendocardial fibrosis and no signs of clinically relevant rejection (International Society for Heart and Lung Transplantation grade 1R; Supplementary Material Figure S1). Donor-specific antibodies (DSAs) were determined, which came back negative.

As the cause of the sudden biventricular failure was unknown, cardiovascular magnetic resonance imaging (CMR) was performed, which showed a left ventricular ejection fraction (LVEF) of 22% and a right ventricular ejection fraction of 35%. Late gadolinium enhancement (LGE) images showed a pattern of extensive subepicardial enhancement and several midwall to subepicardial spots of enhancement of the left ventricle (Figure 1, Supplemental Material Video S1 and S2). Myocardial edema was absent on T2-weighted images and T2 mapping. Furthermore, the native septal T1 value and extracellular volume were normal, indicating no acute rejection (Vermes et al., 2018). The images did not match with abnormalities seen in stress cardiomyopathy (Eitel et al., 2011). The CMR findings were most likely the result of a post-myocarditis state without signs of active myocarditis based on the modified Lake Louis criteria (Ferreira et al., 2018).

Subsequently, a viral myocarditis work-up was initiated on blood (antibody testing, antigen testing, and/or PCR): tests were negative for HIV, hepatitis B virus, hepatitis C virus, hepatitis E virus, and cytomegalovirus. No evidence was found for a recent infection with parechovirus, Parvovirus B19, human herpes virus type 6, Epstein–Barr virus, varicella zoster virus, adenovirus, or enterovirus. PCR on plasma and heart biopsy tested negative for SARS-CoV-2 RNA by RT-PCR. Considering the recent documented SARS-CoV-2 infection, the lack of acute rejection or signs of coronary pathology, and CMR findings, a COVID-19-related post-myocarditis state was suspected as the final diagnosis.

The patient was initiated on heart failure medication, and an implantable cardioverter-defibrillator was implanted due to non-sustained ventricular tachycardias. At discharge, the NT-proBNP had dropped to 49 pmol/l. Two months after discharge, the ejection fraction had partially recovered (LVEF 46%).

Discussion

The first report on heart transplantation patients and COVID-19 originated from China (Wuhan) and described a cohort at the beginning of the pandemic. During this period, no patient had tested positive for SARS-CoV-2 (Ren et al., 2020). However, after this first publication, several single-center studies were published on solid organ transplant recipients in general and specifically heart transplantation patients with COVID-19 (Hoek et al., 2020; Iacovoni et al., 2020; Singhvi et al., 2020). These reports demonstrated a wide range of infection severity, from asymptomatic to ventilator support and even vasopressor support, and varying clinical outcomes. Even a heart transplant recipient needing re-transplantation was reported (Soquet et al., 2020). These findings demonstrate that the follow-up of patients who develop symptoms related to COVID-19 is essential. In a recent Spanish study, acute heart failure was diagnosed in 2.1% of the patients with a SARS-CoV-2 infection without a previous history of chronic heart failure (Rey et al., 2020). The authors argued that due to the restrictive use of non-invasive imaging, this percentage could be an underestimation. Unfortunately, no additional imaging was performed to determine the cause of the acute heart failure due to a lack of resources (Rey et al., 2020). Furthermore, another recently published case report demonstrated a patient with myocarditis late after COVID-19 (Nicol et al., 2020). These findings emphasize the need for close monitoring of cardiac function in the follow-up of patients who have been suffering from SARS-CoV-2.

Recently, a case report was published on a pediatric heart transplant patient who recovered from a SARS-CoV-2 infection but developed de novo DSAs afterwards (Russell et al., 2020). Although this was a single case, treating physicians should always think of acute rejection due to de novo DSAs when a patient has impaired cardiac function. In another study from Brazil that looked at long-term outcomes in heart transplantation patients, the mortality rate was 27.5%; an acute rejection period was seen in 10% and an impaired left ventricular function with unknown cause in 12.5% of patients (Marcondes-Braga et al., 2021). We believe additional imaging should be performed when a clinically significant rejection cannot be proven in a heart transplantation patient with impaired heart function post-SARS-CoV-2 infection, preferably CMR to clarify the cause of the left ventricular dysfunction.

Another study demonstrated a wide range of abnormalities on CMR after a SARS-CoV-2 infection in an unselected and relatively low cardiovascular risk patient population (Puntmann et al., 2020). CMR revealed cardiac involvement in 78 of the 100 patients and even ongoing myocardial inflammation in 60 patients, after resolution of the infection (Puntmann et al., 2020). These abnormalities were independent of the severity of the infection. Endomyocardial biopsies were performed in three patients with

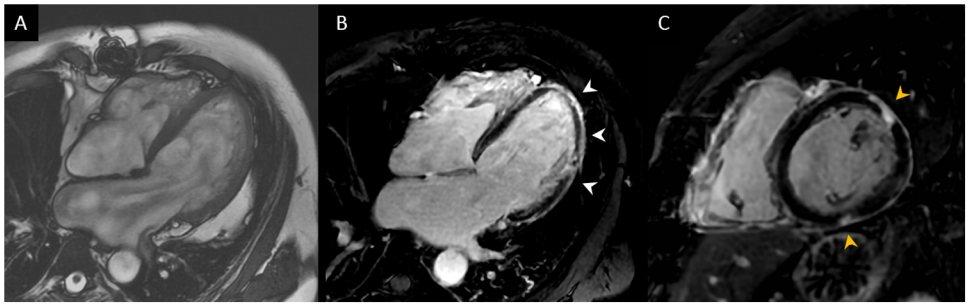

Figure 1. End-diastolic four chamber cine image (A) and four chamber (B) and mid-ventricle short axis (C) late gadolinium enhancement images showing a pattern of extensive subepicardial enhancement (white arrow heads) and several midwall to subepicardial spots of enhancement in the left ventricle (orange arrow heads) consistent with a post-myocarditis state.

severe abnormalities. None of the biopsies detected viral genome, as was the case in our patient (Puntmann et al., 2020). In another study, 26 competitive athletes who had a SARS-CoV-2 infection with no or only mild symptoms had a CMR after quarantine (Rajpal et al., 2021). Of these low-risk patients, four (15%) had signs of myocarditis, confirming that even in these athletes, a relatively large group suffers from myocardial damage (Rajpal et al., 2021). Given the fact that a significant number of these athletes demonstrated abnormalities on CMR, we believe that heart transplant recipients who have suffered from COVID-19 should undergo cardiac evaluation. As a minimum, patients who present with a decrease in cardiac function, pericardial effusion, or raised troponins should have a CMR to determine post-COVID-19 damage.

In conclusion, heart transplantation patients who develop dysfunction of the allograft after a SARS-CoV-2 infection should be screened for acute rejection, DSAs, and cardiac allograft vasculopathy. However, if no substrate for the allograft dysfunction is found, additional testing with CMR should be performed to look for myocardial damage due to SARS-CoV-2-related myocarditis.

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None.

Ethical approval

No ethical approval was needed. Written consent was signed by the patient.

Conflict of interest

JJB declares a grant from Abbott outside the scope of this work. All other authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.04.013.

References

Belsky JA, Tullius BP, Lamb MG, Sayegh R, Stanek JR, Auletta JJ. COVID-19 in immunocompromised patients: a systematic review of cancer, hematopoietic cell and solid organ transplant patients. J Infect 2021;82:329–38.

Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. JAMA 2011;306:277–86.

Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018;72:3158–76.

Hoek RAS, Manintveld OC, Betjes MGH, Hellemons ME, Seghers L, Van Kampen JAA, et al. COVID-19 in solid organ transplant recipients: a single-center experience. Transpl Int 2020;33:1099–105.

Iacovoni A, Boffini M, Pidello S, Simonato E, Barbero C, Sebastiani R, et al. A case series of novel coronavirus infection in heart transplantation from 2 centers in the pandemic area in the North of Italy. J Heart Lung Transplant 2020;39:1081–8.

Jindal V, Sahu KK, Gaikazian S, Siddiqui AD, Jaiyesimi I. Cancer treatment during COVID-19 pandemic. Med Oncol 2020;37:58.

Marcondes-Braga FG, Murad CM, Belfort DSP, Dantas RCT, Lira M, Aragão CAS, et al. Characteristics and outcomes of heart transplant recipients with Coronavirus-19 Disease in a high-volume transplant center. Transplantation 2021;, doi: http://dx.doi.org/10.1097/TP.0000000000003770 Online ahead of print.

Nicol M, Cacoub L, Baudet M, Nahmani Y, Cacoub P, Cohen-Solal A, et al. Delayed acute myocarditis and COVID-19-related multisystem inflammatory syndrome. ESC Heart Fail 2020;7:4371–6.

Patel RH, Acharya A, Chand HS, Mohan M, Byrareddy SN. Human immunodeficiency virus and severe acute respiratory syndrome coronavirus 2 coinfection: a systematic review of the literature and challenges. AIDS Res Hum Retroviruses 2021;37:266–82.

Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, et al. CO-RADS: a categorical CT assessment scheme for patients suspected of having COVID-19-definition and evaluation. Radiology 2020;296:E97–E104.

Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1265–73.

Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiol 2021;6:116–8.

Ren ZL, Hu R, Wang ZW, Zhang M, Ruan YL, Wu ZY, et al. Epidemiologic and clinical characteristics of heart transplant recipients during the 2019 coronavirus outbreak in Wuhan, China: a descriptive survey report. J Heart Lung Transplant 2020;39:412–7.

Rey JR, Caro-Codón J, Rosillo SO, Iniesta Á M, Castrejón-Castrejón S, Marco-Clement I, et al. Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. Eur J Heart Fail 2020;22:2205–15.

Russell MR, Halnon NJ, Alejos JC, Salem MM, Reardon LC. COVID-19 in a pediatric heart transplant recipient: Emergence of donor-specific antibodies. J Heart Lung Transplant 2020;39:732–3.

Sahu KK, Siddiqui AD, Cerny J. COVID-19 pandemic and impact on hematopoietic stem cell transplantation. Bone Marrow Transplant 2020;55:2193–5.

Singhvi A, Barghash M, Lala A, Mitter SS, Parikh A, Oliveros E, et al. Challenges in heart transplantation during COVID-19: a single-center experience. J Heart Lung Transplant 2020;39:894–903.

Soquet J, Rousse N, Moussa M, Goeminne C, Deblauwe D, Vuotto F, et al. Heart retransplantation following COVID-19 illness in a heart transplant recipient. J Heart Lung Transplant 2020;39:983–5.

Vermes E, Pantaléon C, Auvet A, Cazeneuve N, Machet MC, Delhommais A, et al. Cardiovascular magnetic resonance in heart transplant patients: diagnostic value of quantitative tissue markers: T2 mapping and extracellular volume fraction, for acute rejection diagnosis. J Cardiovasc Magn Reson 2018;20:59.

World Health Organisation (WHO). Weekly epidemiological update - 23 March. 2021 (accessed 30 March 2021). https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—23-march-2021.