COVID-19-positivity in a heart transplant recipient—antibody-mediated rejection or SARS-CoV-2-associated cardiac injury?

Paul J. Hanson2,3,*, Felicia Liu-Fei2, Chi Lai3,4, Mustafa Toma5 and Bruce M. McManus1,2,3

1PROOF Centre of Excellence, Vancouver, British Columbia, Canada
2UBC Centre for Heart Lung Innovation, Vancouver, British Columbia, Canada
3UBC Department of Pathology and Laboratory Medicine, Vancouver, British Columbia, Canada
4St. Paul's Hospital, Department of Pathology and Laboratory Medicine, Vancouver, British Columbia, Canada
5St. Paul's Hospital, Division of Cardiology, Vancouver, British Columbia, Canada

*Correspondence address. 166-1081 Burrard St, Vancouver, British Columbia V6Z1B1, Canada. Tel: 604-682-2344 x63544; E-mail: Paul.Hanson@hli.ubc.ca

Abstract

Through the ongoing and heightening coronavirus disease 2019 (COVID-19) pandemic, the heart has been implicated as a central target of injury associated with significantly increased morbidity and mortality. Correspondingly, heart transplant recipients are a vulnerable population for which insufficient research has been conducted. Pathologic antibody-mediated rejection (pAMR) of cardiac allografts shares many characteristics with COVID-19-associated cardiac injury. In this case study, we investigate a 57-year-old female who contracted COVID-19 11 days post-heart transplant and was observed to have pAMR while positive for laboratory-confirmed COVID-19, resulting in a diagnostic conundrum.

INTRODUCTION

Throughout the coronavirus disease 2019 (COVID-19) pandemic, heart transplant (HT) recipients have been faced with innumerable challenges including infection susceptibility, disease exacerbation and treatment. HT recipients have been found to have a 2-fold higher death rate and infection rate for COVID-19 when compared to the general population [1]. Despite current evidence providing an overview of the clinical characteristics of HT patients with COVID-19, there is a gap in pathological research regarding the specific mechanisms of viral infection in these patients. This report follows the unique case of a 57-year-old female who contracted COVID-19 11 days post-HT and developed concurrent pathological antibody-mediated rejection (pAMR). Further investigations have shown the possible role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated cardiac injury presenting similarly to antibody-mediated rejection (AMR), resulting in a diagnostic conundrum.

CASE REPORT

A 57-year-old female with ischemic cardiomyopathy was admitted multiple times to the hospital for heart failure and cardiogenic shock in 2020. In July 2020, an echocardiogram showed a left ventricular ejection fraction of 11%. The patient was known for atrial fibrillation, type 2 diabetes mellitus, chronic kidney disease, transient ischemic attack and chronic obstructive pulmonary disease. She was an ex-smoker of 30-pack-years who quit 6 months prior to transplant. Her family history was notable for coronary artery disease, with her father and grandfather having experienced myocardial infarctions in their 60s.

In December 2020, the patient received a HT. On 6 January 2021 (11 days later), she tested positive for COVID-19 due to an in-hospital outbreak. A week following, she developed increased oxygen requirements and a right-sided pleural effusion on chest computed tomography (CT). Although the patient noted shortness of breath when lying flat or with movement, she was not in acute respiratory distress and was hemodynamically stable with normal heart function on echocardiography. Despite initially being diagnosed with pAMR of the cardiac allograft (Fig. 1), subsequent investigations have suggested a potential presentation of COVID-19 infection resembling pAMR in the heart of this patient (Fig. 2).

Prior to transplantation, the patient had 0.1% HLA I and 63.2% HLA II. At the time of transplant, the patient...
Figure 1. Immunohistochemical staining of patient biopsies. Immunohistochemical staining images of consecutive patient biopsies for SARS-CoV-2 spike protein, CD68, C4d and CD31. SARS-CoV-2 images are at 10×, and SARS-CoV-2 positivity in the myocardium is highlighted with 40× inserts. C4d and CD31 images are at 10×, CD68 images are at 20×.

Figure 2. PAMR H&E. Pathologic antibody-mediated rejection (pAMR) shows distended capillary-sized blood vessels with intravascular macrophages and reactive endothelial cells as shown in these representative H&E photomicrographs (original magnification, 600×).

had a moderate (mean fluorescence intensity = 4149) DSA to HLA DPB1∗04:01 detected. The B-cell flow cross-match was reported to be negative; although the B-cell shift was below the threshold level of 80, the shift toward the positive cutoff was consistent with the moderate donor-specific antibody to DP0401. Immunohistochemistry detected positive staining for the SARS-CoV-2 spike protein in the explanted recipient heart tissue despite a negative nasopharyngeal swab test. Following cardiac transplant, the patient tested negative for SARS-CoV-2 on 4 January 2021, and positive for SARS-CoV-2 on 6 January. The patient’s 4 January post-transplant biopsy showed no acute cellular rejection (grade 0R) and immunohistochemical evidence of pAMR1(I+). An echocardiogram revealed improving cardiac function from the time of transplant.

After her COVID-19 diagnosis, the patient became increasingly hypoxemic but was otherwise hemodynamically stable with normal heart function by echocardiogram. The patient was prescribed dexamethasone from 10–23 January for COVID-19. The pAMR in her cardiac allograft appeared to become more persistent as her hospital stay progressed. On 20 January and 27 January, cardiac allograft biopsies showed pAMR2, which slowly resolved until the patient was discharged on 26 February. Given her stability on echocardiogram, she was not treated for pAMR. Compared to the CT-chest on 12 January, which showed a ground-glass lung phenotype consistent with COVID-19 pneumonia, the 26 January CT-chest demonstrated marked recovery. The patient tested positive again for SARS-CoV-2 on 7 February, via nasopharyngeal swab. The reports of transplant rejection were congruent with COVID-19 positivity and diminished with viral clearance.

At discharge, she was taking multiple medications, including tacrolimus, prednisone, mycophenolate, acetylsalicylic acid and pravastatin. Neither intubation nor mechanical ventilation was required throughout her hospital stay. At the time of her 10 March biopsy, she had no evidence of pAMR.

DISCUSSION

Allograft rejection is responsible of 10% of deaths within the initial 3 years after transplant [2], and COVID-19 patients with cardiac injury have a 51.2% increase in-hospital mortality compared to those without [3]. Although there are no current studies on the combination of pAMR and COVID-19, it is hypothesized that
worse outcomes will be documented, warranting further investigation. PAMR is typically treated with the goal to stop immune-mediated injury and supporting cardiac failure [4]. Although there is no current diagnostic consensus, corticosteroids and intravenous gamma globulin have widely been reported as therapeutics [4]. For severe COVID-19 manifestations, antivirals, anticoagulation and immunosuppressive therapy (e.g. corticosteroids, IL-6 inhibitors, JAK 1,2 inhibitors) are often prescribed [5]. Corticosteroids contribute to T-cell and B-cell suppression though the specific effects of dexamethasone on pAMR remain to be elucidated [4].

The criteria for pAMR2 requires histological (capillary endothelial swelling and macrophages within capillaries) and immunopathologic (C4d) findings [4]. Correspondingly, these indicators are also characteristic of COVID-19-associated cardiac injury.

Although C4d is a marker of pAMR, research also implicates this protein as a hallmark of COVID-19-mediated infection. Deposits of C4d have been found in the heart, lung, brain, skin and liver tissue which is compatible with SARS-CoV-2 spike protein and RNA localization and ACE2 receptor presence in severe COVID-19 patients [6, 7]. Control patients had no deposits, while all COVID-19 tissue examined were positive for C4d7.

Macrophages, characterized by CD68 expression and a vital component in AMR diagnosis, have been found to play a prominent role in COVID-19 pathogenesis. Various mechanisms, including macrophage activation syndrome and cytokine storm, have been reported in the hearts of COVID-19 patients and contribute to thrombosis [8]. Capillary endothelial changes (CD31) have also been observed in COVID-19 patients. Compared to controls, COVID-19 positive patients were found to express high levels of the SARS-CoV-2 cellular receptor ACE2 in capillaries, consistent with findings of endotheliitis and inflammation [9].

Based on current research regarding the role of C4d, macrophages and capillary endothelial changes in COVID-19 pathogenesis in the heart (Fig. 2), in addition to reports of AMR consistent with SARS-CoV-2 positivity (Fig. 1), an enigma has been presented regarding the role of COVID-19 in the clinical presentation of this patient.

CONFLICT OF INTEREST STATEMENT
None declared.

ETHICAL APPROVAL
None required.

CONSENT
Written consent obtained.

GUARANTOR
P.H. is nominated as the manuscript’s guarantor.

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