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Accelerated Cardiac Allograft Vasculopathy in an Orthotopic Heart Transplant Recipient with Prior COVID-19

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Data Interpretation D
Manuscript Preparation E
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Patient: Male, 48-year-old
Final Diagnosis: Cardiac amyloidosis
Symptoms: Abdominal pain • dyspnea • palpitation
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare coexistence of disease or pathology

Background: Cardiac allograft vasculopathy (CAV) is a post-orthotopic heart transplant (OHT) complication driven by intimal smooth muscle proliferation and immune hyperactivity to donor heart tissue. Accelerated CAV leads to allograft failure within 1 year after receiving a normal angiogram result. Viruses can contribute to CAV development, but CAV after SARS-CoV-2 infection has not been reported to date.

Case Report: A 48-year-old man, 5 years after OHT for non-ischemic cardiomyopathy, was admitted to the Cardiac Care Unit with 3 days of abdominal pain, dyspnea, and palpitations. His medical history included hyperlipidemia and insulin-dependent diabetes. He was compliant with all medications. Two months prior, he had a mild COVID-19 case. An echocardiogram and coronary angiogram 6 and 9 months prior, respectively, were unremarkable. Right and left heart catheterization demonstrated increased filling pressures, a cardiac index of 1.7 L/ml/m^2, and diffuse vasculopathy most severe in the LAD artery. Flow could not be restored despite repeated ballooning and intra-catheter adenosine. Empiric ionotropic support, daily high-dose methylprednisolone, and plasmapheresis were started. A few days later, the patient had cardiac arrest requiring venoarterial extracorporeal membranous oxygenation. Given CAV's irreversibility, re-transplantation was considered, but the patient had an episode of large-volume hemoptysis and remained clinically unstable for transplant. The patient died while on palliative care.

Conclusions: Our patient developed accelerated CAV 2 months after having COVID-19. While CAV has known associations with certain viruses, its incidence after SARS-CoV-2 infection is unknown. Further research is needed to determine if prior SARS-CoV-2 infection is a risk factor for development of CAV in OHT recipients.

Keywords: Autoimmunity • COVID-19 • Graft Rejection • Heart Transplantation • Transplantation Tolerance
Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/937955

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Background

Cardiac allograft vasculopathy (CAV) is a serious complication for orthotopic heart transplant (OHT) recipients. The pathophysiology of CAV is thought to be due to the recipient's immune system reacting to the donor's foreign heart tissue, leading to concentric fibromuscular hyperplasia of the intima of the coronary vasculature of the transplanted heart [1]. CAV can be devastating for many OHT recipients as its onset can be early, presenting within years of the transplant, and is pervasive and angiographically detectable in approximately one-third of OHT patients within 5 years and in almost half within 10 years [2]. CAV is difficult to manage, with no strongly effective treatment, often leading to aggressive percutaneous coronary intervention or redo heart transplantation. Accelerated CAV is characterized by an even worse prognosis, leading to allograft failure within 1 year [2]. The risk of CAV is increased by traditional, non-immunogenic risk factors (eg, age, obesity, male sex, diabetes, and hyperlipidemia), immunologic risk factors, and donor-specific risk factors [3]. Notably, viruses such as cytomegalovirus (CMV) and hepatitis C virus (HCV) have also been implicated in CAV. Acute COVID-19, due to infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been associated with increased risk of mortality for OHT recipients [4,5], but to date, no association has been demonstrated between SARS-CoV-2 infection and CAV. We report, to the best of our knowledge, the first case of accelerated CAV in an OHT recipient after COVID-19 [6].

Case Report

A 48-year-old man with a history of non-ischemic cardiomyopathy status-post OHT 5 years prior presented to the Emergency Department with a 3-day history of palpitations, shortness of breath, and chest and epigastric pain [6]. His past medical history was notable for an OHT (donor and recipient were CMV- and HCV-negative), insulin-dependent diabetes, and hyperlipidemia. His post-transplant course was notable for only 1 episode of resolved acute cellular rejection early after transplantation and mild COVID-19 illness, defined as COVID-19 not requiring anti-viral medication or hospitalization, 2 months prior to presentation. He was adherent to his immune suppression regimen, which included tacrolimus and mycophenolate. He also took aspirin, glimepiride, metformin, rosuvastatin, and fluconazole. He was unvaccinated against COVID-19. He reported no use of tobacco, alcohol, or recreational drugs. Echocardiograms and coronary angiograms were obtained annually for monitoring of the transplanted graft. The echocardiogram obtained 6 months prior, and all previous echocardiograms, were normal except for mild mitral regurgitation and mild concentric left ventricular hypertrophy. All prior coronary angiograms including the latest, from 9 months prior, obtained for annual screening of the transplanted graft, showed no significant epicardial coronary artery disease. His vital signs were notable for an increased heart rate of 130 beats per minute, a blood pressure of 124/96 mmHg, a respiratory rate of 26, and an oxygen saturation of 94% on room air. His physical exam was notable for distended neck veins and right upper quadrant and epigastric pain. He was fully alert and oriented. Initial laboratory studies revealed a normal complete blood count and normal renal function. Non-anion gap metabolic acidosis and elevations in transaminases were present. Serum troponin I was elevated to 10.6 ng/ml (normal <0.04 ng/ml). Tacrolimus level was within his therapeutic goal. Electrocardiogram showed junctional tachycardia.

The patient was given 1 liter of intravenous (IV) fluids, aspirin 325 mg, acetaminophen 1 gm, and morphine 4 mg IV. He then underwent an expedited right and left heart catheterization. Mean pulmonary artery pressure was 37 mmHg, and cardiac index was calculated at 1.7 L/min/m^2 and 1.6 L/min/m^2 by thermodilution and Fick methods, respectively. Angiographic evaluation of the coronary arteries was notable for diffuse vasculopathy with severe disease in the first obtuse marginal branch, first diagonal artery, and the apical left anterior descending (LAD) artery (**Figure 1**). The right coronary artery (RCA) also showed signs of vasculopathy and had 20% stenosis. Flow was unable to be restored to the LAD artery despite attempts at ballooning and administration of intra-coronary adenosine.

Methylprednisolone 500 mg daily and a milrinone 0.2 mcg/kg/min infusion were started. The next day, an endomyocardial biopsy was obtained, which revealed pAMR1 antibody-mediated rejection without evidence of acute cellular rejection. Plasma exchange was then initiated for a planned 5-day course. Methylprednisolone was transitioned to a prednisone taper. The patient appeared to improve and milrinone had begun to be weaned when he had a cardiac arrest with pulseless electrical activity initially then ventricular fibrillation. Advance cardiovascular life support was performed for 30 minutes until venoarterial extracorporeal membrane oxygenation (ECMO) could be initiated. Following ECMO, the patient's course was complicated by large-volume hemoptysis, multiple episodes of ventricular arrhythmia, and severely elevated pulmonary pressures.

Over the next several days the patient's mental status improved, and he was extubated. However, he then experienced recurrent large-volume hemoptysis. A bronchoscopy revealed diffuse alveolar hemorrhage presumed to be secondary to elevated pulmonary pressures in the setting of continued acute heart failure. Unfortunately, his hemoptysis was not able to be controlled and he was considered too unstable for cardiac transplantation. The patient died on hospital day 29 after transitioning to palliative care. **Figure 2** summarizes the timeline of events.

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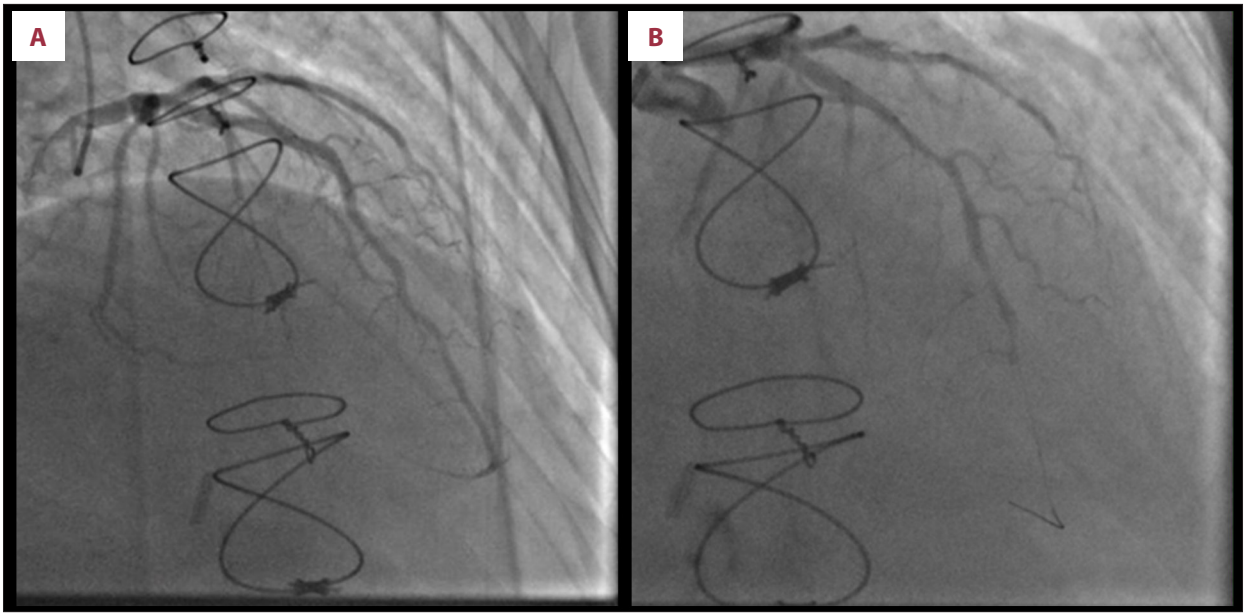

Figure 1. Coronary angiography comparison. (**A**) Coronary angiogram from 9 months prior to presentation, showing mild cardiac allograft vasculopathy without any significant stenosis. (**B**) Coronary angiogram from the current presentation, showing diffuse cardiac allograft vasculopathy that has progressed significantly from the prior angiogram. The apical portion of the left anterior descending artery is completely occluded. Multiple attempts at balloon angioplasty were unsuccessful.

Time	Event
(-) 5 years	Orhtotopic heart transplantation for non-ischemic cardiomyopathy
(-) 6-9 months	Coronary angiogram without epicardial coronary artery disease and stable echocardiogram
(-) 2 months	Mild COVID-19 infection
Presention (Time 0)	Emergency Department Symptoms: Dyspnea, palpitations, chest & epigastric pain ×3 days Vital signs: Heart rate 160, blood pressure 124/96 mmHg, respiratory rate 26, SPO2 94% on room air Exam: Distended neck veins, abdominal pain
Hospital Day (HD) 1	Underwent expedited left and right heart catherization Coronary angiogram: Diffuse vascolupathy of left anterior descending (LAD) artery and 20% right coronary artery stenosis. Ballon angiography attempted of LAD attempted but was unsuccesful Cardiac index 1.7 L/min/m^2, right atrial pressure 17 mmHg, pulmonary artery pressure 41/37 mmHg
	Initial management: Methyprednisolone 500 mg daily, milrinone continous infusion
HD 3	Endomyocardial bioipsy: Antibody mediated rejection without evidence of acute cellular rejection Subsequent management: 5-day plasma exchange, methylprednisone to prednisone taper, milrinone tapered
HD 8	Cardiac arrest with pulselles electrical activity then ventricular fibrillation prompting extracorporeal membrane oxygenation initiation. Redo transplantation pursued
HD 29	Large volume hemoptysis, ventricular arrhytmias, and elevated pulmonary pressures Goals of care discussion: Unable to control hemoptysis, transition to comfort oriented care
Post-mortem	Autopsy biopsy requested: Severe cardiac allograft vasculopathy with 90% stenosis of LAD, LCX, and RCA arteries and circumferential acute myocardial of the left ventricle

Figure 2. Detailed timeline of events.

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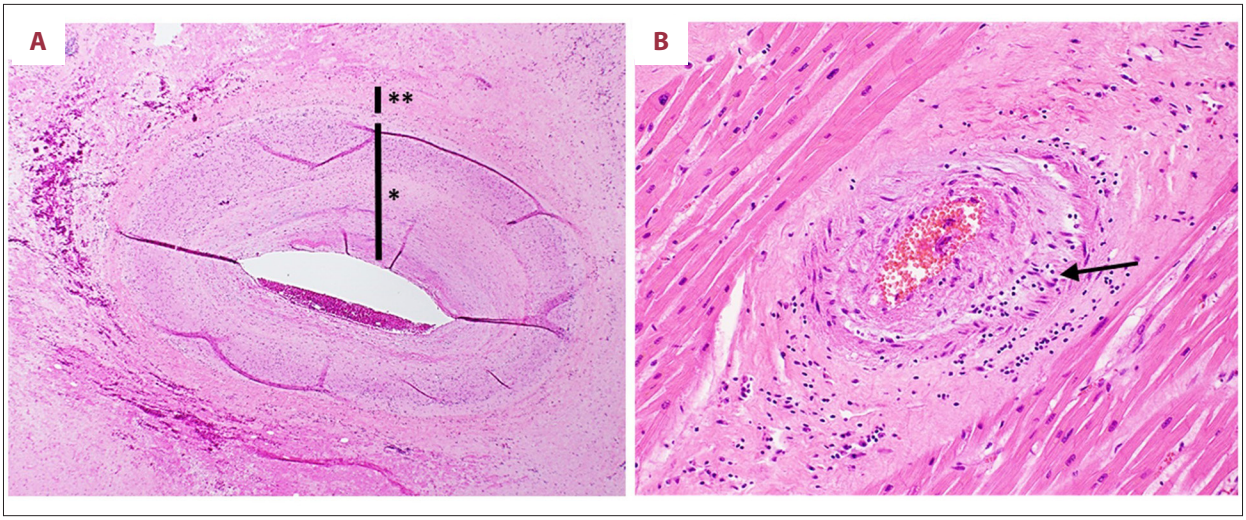

Figure 3. Severe cardiac allograft vasculopathy. (**A**) Proximal left anterior descending artery; concentric proliferation of the intima (*) that spares the elastic lamina (**) (Hematoxylin and eosin staining [H&E], 40× magnification). (**B**) Intramyocardial artery with intimal proliferation and sparse mural chronic inflammation (arrow) (H&E, 200× magnification).

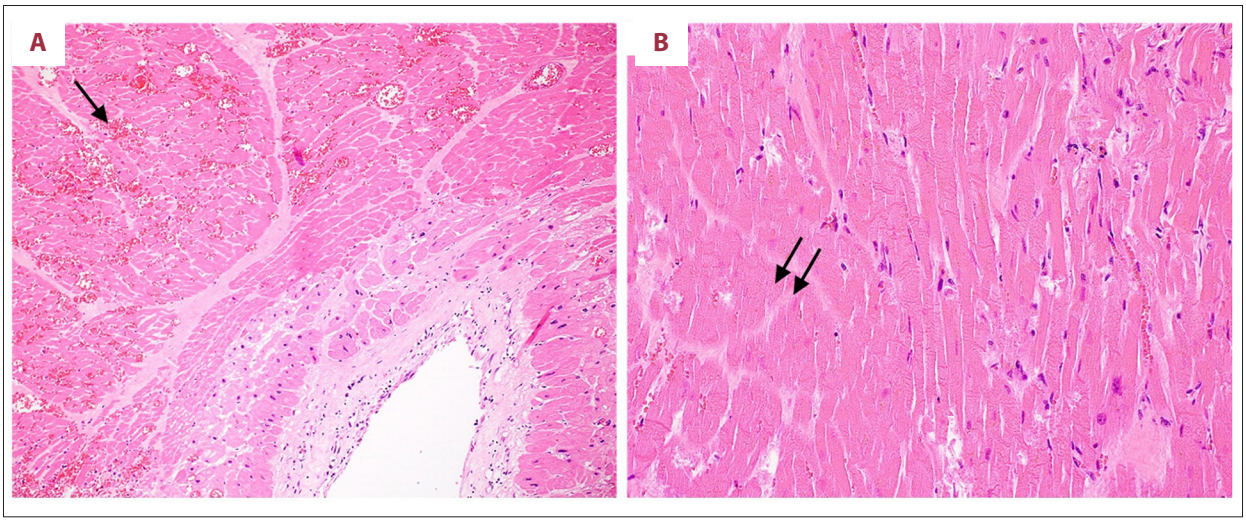

Figure 4. Acute myocardial infarction. (**A**) Myocardium with coagulative necrosis and hemorrhage (arrow), with subendocardial sparing (H&E, 40× magnification). (**B**) High-power view of the myocytes displaying contraction band necrosis, hypereosinophilia and loss of nuclei (double arrow) (H&E, 200× magnification).

The family requested an autopsy study, which revealed severe cardiac allograft vasculopathy and acute myocardial infarction. All epicardial coronary arteries and their branches showed involvement of CAV, with maximally up to 90% stenosis of the distal LAD artery, left circumflex artery, and RCA. Microscopic examination showed concentric intimal proliferation of the LAD artery with sparing of the elastic lamina, and an intramyocardial artery with intimal proliferation and sparse mural chronic inflammation (**Figure 3**). The myocardium showed near-circumferential, subendocardial-sparing coagulative necrosis of the left ventricle, with hypereosinophilic cytoplasm, loss of nuclei, edema, hemorrhage, and focal inflammation, consistent with acute myocardial infarct from global ischemia (**Figure 4**). There was no evidence of acute cellular rejection or antibody-mediated rejection. The lungs showed patchy organizing pneumonia with evidence of acute hemorrhage.

Discussion

We describe a case of accelerated CAV that developed several years after initial transplantation, possibly attributable to the patient's recent mild COVID-19 infection. We discuss how in the context of normal diagnostic testing 6-9 months prior to the development of CAV, the patient's recent COVID-19 may have contributed to his rapid progression of CAV, leading to

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death. We also review the latest evidence for the detection and management of CAV.

COVID-19 illness can present with a wide range of clinical outcomes. Given their immunosuppressed status, OHT recipients faced COVID-19-related fatality rates of up to 25-30% prior to widespread vaccination efforts [4,5,7,8]. CAV may increase the risk of mortality from COVID-19 in OHT recipients, but whether COVID-19 can precipitate accelerated CAV remains unknown.

CAV most commonly progresses over years following a transplant, with 8% of patients having angiographically detectable CAV within 1 year, 32% within 3 years, and 43% within 10 years, thus allowing time for detection and treatment [2]. In contrast, accelerated CAV classically develops within 1 year after an inciting event or trigger and in some cases can occur within months of a normal angiogram [9]. CAV is thought to be driven by endothelial cell injury triggering host immune factor recruitment, which in turn leads to smooth muscle proliferation in the intima of the vessel wall. Identified triggers of cell injury include viral infections and ischemia-reperfusion injury, as well as classic risk factors such as hyperlipidemia, diabetes, and hypertension [10,11]. It is unclear what causes acceleration of the rate of CAV.

In our case, the patient was 5 years post-transplantation and had a completely normal angiogram and echocardiogram 9 and 6 months prior, respectively, before presenting with cardiogenic shock due to severely stenosed coronary arteries. Given the temporal distance from his transplant, rapid progression at this time point was unusual, although his pre-existing hyperlipidemia and diabetes may have increased his risk. Additionally, although not yet associated with CAV, it is possible the patient's SARS-CoV-2 infection 2 months prior may have represented an inciting trigger for the rapid development of CAV. In other words, in this vulnerable patient with pre-existing risk factors for the development of CAV, the patient's recent infection with SARS-CoV-2 may have catalyzed the accelerated development of CAV.

On endomyocardial biopsy, accelerated CAV may present with concentric intimal proliferation and inflammation resulting in an almost 100% luminal occlusion within intramyocardial coronary microvessels [12]. Histologically, the hallmarks of accelerated CAV include active intimal and transmural vasculitis, peri-adventitial inflammation, and in some cases, shallow mural thrombus [9]. Autopsy of our patient showed similar findings, although no mural thrombus was present.

While no direct evidence implicates COVID-19 in the development of accelerated CAV, COVID-19-induced graft dysfunction has been associated with corneal, kidney, liver, and lung transplants.

In a 32-year-old man with a prior keratoplasty and COVID-19, Singh and Mathur describe the mechanism behind acute graft rejection of the corneal transplant as initial invasion via attachment to specific angiotensin-converting enzyme-2 (ACE2) receptors present in corneal and conjunctival epithelium, followed by "cytokine storm" [13]. This form of immune system dysfunction presenting as overproduction of proinflammatory markers such as interleukin (IL)-1, IL2, IL-6, and tumor necrosis factor (TNF)-α and an increased rate of differentiation to CD4+ T lymphocytes overwhelmed the natural immune regulation of the cornea, resulting in graft destruction [13].

Similarly, 2 patients with COVID-19 after kidney transplant had elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate, and IL-6, suggesting a hyperinflammatory state in the development of graft dysfunction [14,15]. This phenomenon of allograft rejection following COVID-19 was also described in liver transplant patients. However, to the best of our knowledge, no study has yet described the development of lung allograft failure after COVID-19 infection despite the virus's predilection for the lung and the presence of elevated serum D-dimer, IL-6, lactate dehydrogenase, and CRP in this population [16,17]. Our patient acquired a mild SARS-CoV-2 infection (not requiring anti-viral medications or hospitalization). In greater than 50% of cases of mild COVID-19, inflammatory markers (eg, IL-6, CRP, ferritin) are elevated; therefore, our patient may have developed CAV secondary to the inciting inflammation from COVID-19 [18,19].

Potential Mechanisms for COVID-19-Induced Accelerated CAV

After heart transplantation, patients are placed on an immunosuppressive pharmacologic regimen to prevent the development of CAV mediated by an immune response to the donor's foreign heart tissue. This regimen usually includes a calcineurin inhibitor (eg, tacrolimus), mycophenolate, and occasionally a proliferation signal inhibitor (eg, sirolimus or everolimus) [2]. Unfortunately, this intentional suppression of the immune system can predispose OHT recipients to contract COVID-19 via a reduced ability to combat the infection.

When SARS-CoV-2 infects the susceptible host, evidence suggests that the virus enters endothelial cells via binding of its spike protein to the ACE2 receptor in tissues with high ACE2 expression, such as the heart [20,21]. Endothelial cells normally participate in inflammatory reactions and procoagulant responses, but ACE2-mediated entry of SARS-CoV-2 into endothelial cells can cause endothelial overactivation and dysfunction [21].

Specifically, COVID-19-induced endothelial dysfunction can lead to increased autoimmunity via overactivation

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of proinflammatory cytokines such as IL-1, IL-2, IL-6, and TNF-α [13]. This cytokine storm results in an inflamed endothelium, increased vessel permeability, a hypercoagulable state, and excessive leukocyte chemotaxis [21].

In fact, studies have shown that increasing levels of circulating endothelial cells in COVID-19 patients are directly correlated with increased proinflammatory cytokines from acute infection through the recovery phase, suggesting that endothelial dysfunction not only leads to production of cytokines but is also propagated by cytokines [22].

Although these changes may be reversible initially, in the setting of persistent endothelial dysfunction the increased immune response to donor tissue can lead to development of intimal proliferation, increased intimal thickness, and luminal occlusion characteristic of CAV.

Importantly, the mechanism outlined above can be induced by both mild and severe cases of COVID-19. Serologic testing of patients with mild and severe COVID-19 have yielded significantly higher levels of proinflammatory cytokines such as IL-6, CRP, and TNF-α compared to healthy controls more than 50% of the time [18,19]. It is unknown at this time whether vaccination against COVID-19 can protect patients from possible COVID-19-induced CAV, but vaccination has been shown to decrease infection severity in both immune-competent and immune-compromised populations [23].

Taken together, these potential mechanisms may explain why our patient, given his immune-suppressed state after transplant along with pre-existing risk factors for CAV (eg, insulin-dependent diabetes and hyperlipidemia), may have developed an accelerated case of CAV incited by his recent SARS-CoV-2 infection.

We acknowledge the above-average rate of infection with SARS-CoV-2 in heart transplant recipients given their immunosuppressed state; however, we report the first known case of accelerated CAV development after SARS-CoV-2 infection in an OHT recipient. We can only speculate as to why this phenomenon is not more common. It is possible that many OHT recipients who contract SARS-CoV-2 die from COVID-19-related complications prior to the development of CAV. It is also possible that the temporal relationship between COVID-19 and CAV has gone unrecognized or been under-detected. Or it could simply be that, despite the increased probability of COVID-19 in OHT recipients, infection with SARS-CoV-2 inciting the development of CAV is rare. This demonstrates a need for further investigation into the relationship between COVID-19 and CAV, especially given the established link between other viral illnesses and the consequent development of CAV.

Mechanism for Other Viruses and CAV

Other viral agents have also been implicated in the development of accelerated CAV, including herpes-simplex virus-1 (HSV-1), herpes-simplex virus-2 (HSV-2), Epstein-Barr virus (EBV), and CMV. These viruses, and even bacteria such as *Chlamydia pneumoniae* and *Helicobacter pylori*, are associated with increased cardiovascular risk and levels of CRP, and an increasing total pathogen load is an effective predictor of severity of risk [12,24]. Acute CMV infection specifically can induce inflammation within the subendothelial wall of the allograft, leading to enhanced allograft dysfunction and rejection [25]. After this phenomenon was observed clinically, researchers were able to replicate an acute infection with CMV in rats, demonstrating that an early inflammatory response in the adventitia and intima of the aorta and cardiac allograft resulted in increased intimal thickness and increased luminal occlusion. These changes are driven by increased leukocytes and cytokines, accelerating acute allograft rejection [26]. Additionally, there is also evidence that hearts from HCV-positive donors have an increased rate of CAV at 1 year after transplant [27].

Detection and Management of CAV

The symptomatology of CAV is wide-ranging, and most patients do not present acutely. Rather, patients may be largely asymptomatic, with CAV often found incidentally. Therefore, diagnosis must be based on more than just clinical criteria [3]. Coronary angiography with or without intravascular ultrasound (IVUS) imaging remains the initial test for diagnosis of CAV, with a positive finding defined as a maximal intimal thickness of greater than or equal to 0.5 mm [28]. Optical coherence tomography also can play an important role in determining the progression of CAV [29].

Non-invasive modalities include dobutamine stress echocardiography (DSE), radionuclide myocardial perfusion imaging utilizing either positron emission tomography or single-photon emission computed tomography (CT), coronary CT angiography, and cardiac magnetic resonance imaging [30]. While these modalities are all gaining popularity, they demonstrate only a modest sensitivity and specificity in a handful of studies and further research is necessary to adequately judge their utility in CAV diagnosis.

Prevention of CAV begins with immunosuppression immediately after transplant, typically with a calcineurin inhibitor and mycophenolate mofetil [31]. Control of hypertension and diabetes is also crucial [31]. Notably, statin therapy has become a mainstay for CAV prevention by reducing the incidence of allograft rejection and progression of CAV through anti-inflammatory, immunomodulatory, and cholesterol-lowering effects [32,33]. When accompanied with acute antibody or cellular rejection, management of CAV may include additional treatment with

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high-dose steroids, intravenous immunoglobulin, thymoglobulin, and plasmapheresis [34]. Percutaneous coronary intervention may provide temporary benefit by revascularizing stenotic focal lesions, but CAV generally results in diffuse and progressive disease [28]. Redo OHT is most often the only definitive treatment [28]. Many of these strategies were attempted in our patient, but unfortunately were insufficient to prevent cardiac failure from stenosed coronary arteries. Additionally, clinical instability precluded redo OHT in this case.

Conclusions

CAV remains a major cause of morbidity and mortality in the years following successful OHT. We describe, to the best of our knowledge, the first reported case of possible COVID-19-induced accelerated CAV in an OHT patient with pre-existing risk factors for CAV and review the pathophysiology, detection, and management of this disease. Further research into the early diagnosis and prevention of CAV is necessary to ensure that OHT recipients are correctly managed in the era of COVID-19 and in the face of many other viral infections, which demonstrate a clear and present danger to this immunosuppressed population.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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