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CASE REPORT

A Fatal Case of COVID-19 Pneumonia in a Fully Vaccinated Heart Transplant Recipient

Agastya D. Belur[1], MD; Diana Otero Mostacero[1], MD; Christina L. Dunbar-Matos[2], DO MPH MS FACC*

[1]Cardiovascular Medicine Fellowship Program, University of Louisville School of Medicine, Louisville, KY, USA; [2]Division of Cardiovascular Medicine, University of Louisville School of Medicine, Louisville, KY, USA

*agastya.belur@louisville.edu

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Abstract

The development and administration of mRNA vaccines against SARS-CoV-2 are seeing lower numbers of COVID-19 cases and fatalities among fully vaccinated, immunocompetent adults. We present a case of fatal COVID-19 pneumonia in a heart transplant recipient who had received two doses of mRNA COVID-19 vaccine before the Centers for Disease Control and Prevention had recommended additional doses.

Introduction

See editorial commentary on this article.

In healthy individuals, exogenous mRNA such as that used in the BNT162b vaccine stimulates strong induction of potent inflammatory cytokines, which elicit T- and B-cell-mediated immune responses.[1] An interim analysis of the phase III trial showed that the BNT162b vaccine conferred 95% protection against infection in persons 16 years of age or older who had received a two-dose regimen.[2] However, key exclusion criteria for this study included a history of treatment with immunosuppressive therapy or diagnosis with an immunocompromising condition.[2] Although the vaccine is safe, data on its efficacy in transplant recipients are mixed and are a topic of ongoing clinical investigation.

Case Description

A 71-year-old male presented with two days' shortness of breath, myalgias, and chills in March 2021, before the Centers for Disease Control and Prevention (CDC) had recommended third and fourth doses of the mRNA vaccine. Vital signs on admission included a temperature of 99.0 °F, heart rate of 108 beats/minute, blood pressure of 137/86 mmHg, respiratory rate of 17 breaths/minute, and oxygen saturation ranging from 88 to 96% on 3L O_2 through nasal cannula. He was in mild respiratory distress, with otherwise unremarkable physical examination. Laboratory exams were significant for lymphopenia, with an absolute lymphocyte count of 500/μL and acute kidney injury (AKI), with a serum creatinine of 3.0 mg/dL. Procalcitonin level was 0.17 ng/mL. His brain natriuretic peptide (BNP) level was found to be elevated at 235 pg/mL. A chest X-ray showed cardiomegaly with pulmonary vascular engorgement (**Figure 1**), and an electrocardiogram showed an atrial-sensed, ventricular-paced rhythm with a ventricular rate of 86 beats/minute (**Figure 2**).

The patient had received two doses of the COVID-19 vaccine four weeks apart, with the second dose 16 days prior to admission.

Medical history

The patient received an orthotopic heart transplant in 2008, with his most recent endomyocardial biopsy in March 2016 (5 years prior to current presentation) showing an International Society for Heart & Lung Transplantation scale score of 0R. This biopsy, eight years after the transplant, was performed to rule out rejection because the patient was experiencing shortness of breath and fatigue at the time. Multiple other biopsies in the past were unremarkable. He also had a history of obesity (body mass index [BMI] 46.2), hypertension, unprovoked deep vein thrombosis, and dual chamber pacemaker implantation for

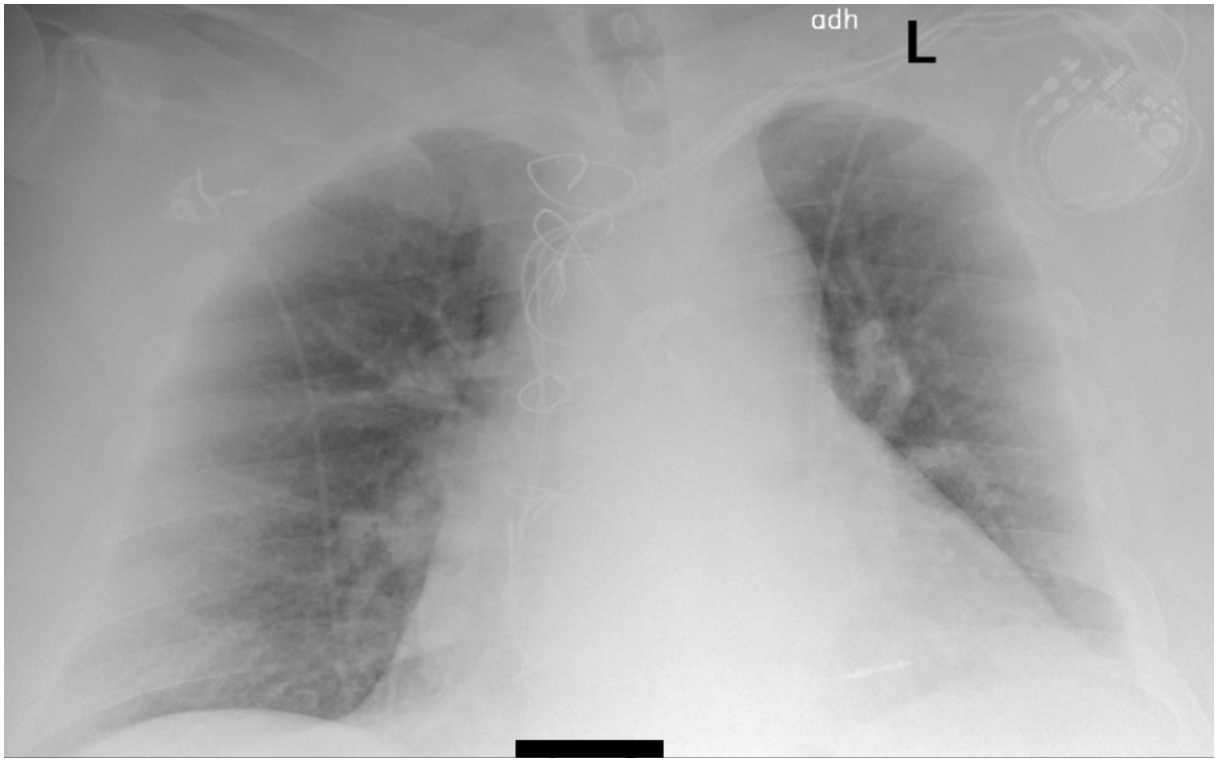

Figure 1. Chest X-ray on admission showing cardiomegaly with pulmonary vascular engorgement.

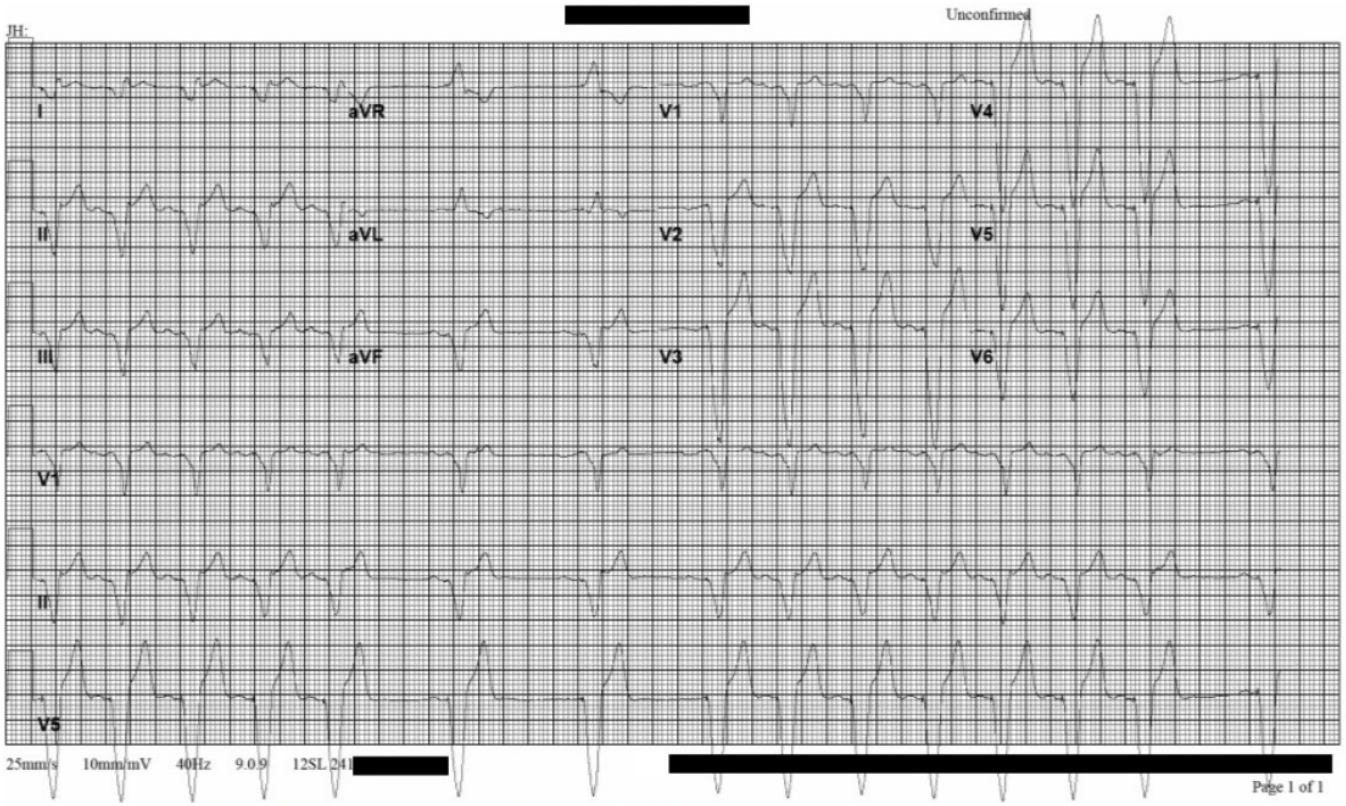

Figure 2. Electrocardiogram on admission showing an atrial-sensed, ventricular-paced rhythm.

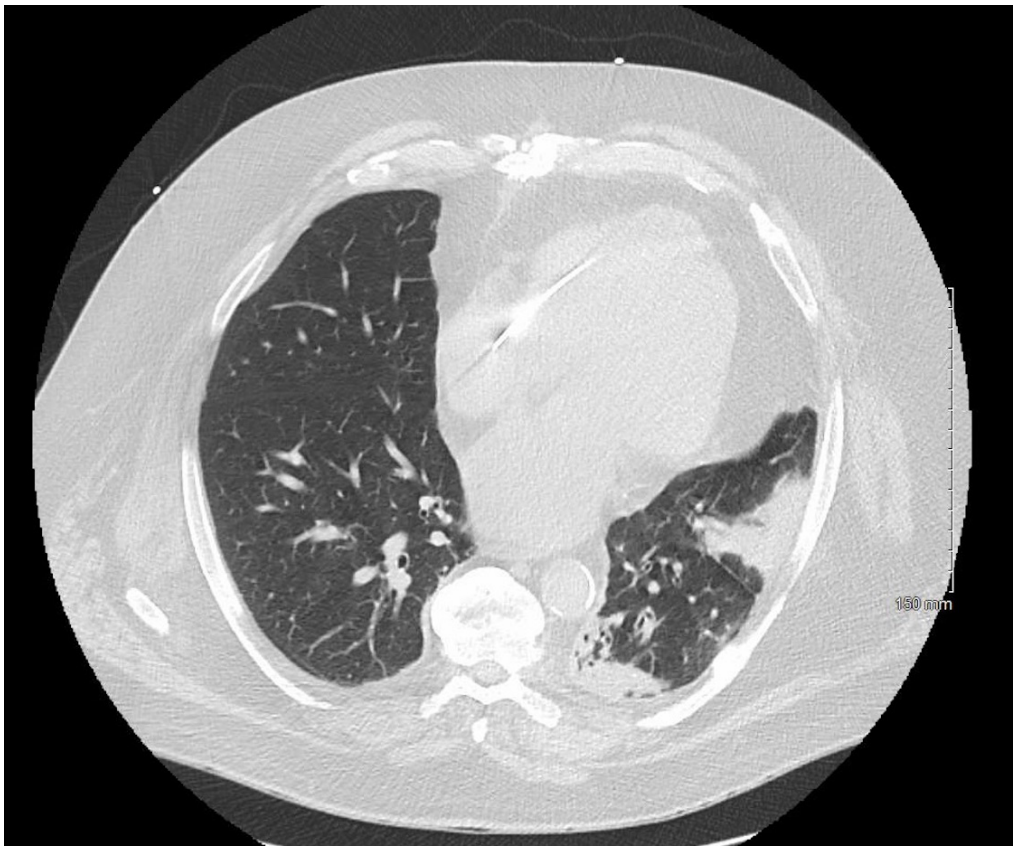

Figure 3. Chest computed tomography showing left lower lobe atelectasis.

symptomatic bradycardia. The pacemaker implant was likely related to loss of sympathetic tone of his transplanted heart, and unfortunately, additional details related to his history of symptomatic bradycardia are unknown. His home medications included mycophenolate mofetil 1,250 mg PO BID and tacrolimus 2 mg PO daily for immunosuppression, amlodipine 5 mg, lisinopril 40 mg, and warfarin 7 mg daily.

Differential diagnosis included COVID-19 pneumonia, other viral pneumonia, pulmonary embolus, acute bacterial pneumonia, transplant rejection, and heart failure exacerbation.

Investigations

A nasopharyngeal swab was positive for SARS-CoV-2 on admission. Initial infectious workup, including nasopharyngeal swab for methicillin-resistant *Staphylococcus aureus*, viral respiratory panel, and urine studies for *Streptococcus pneumoniae* and legionella antigens, was negative. High-sensitivity C-reactive protein was elevated at 18.43 mg/L (reference range 0–4 mg/L). Interleukin-6 levels were markedly elevated at 301.16 pg/mL (reference range $<$5 pg/mL). Other markers of inflammation, such as lactate dehydrogenase, D-dimer, and ferritin, were within normal limits.

Further investigations revealed a therapeutic tacrolimus level of 6.8 ng/mL (reference range 5–20 ng/mL). A computed tomography (CT) scan of the chest with contrast showed bilateral lower lobe atelectasis with scattered reactive mediastinal and hilar lymph nodes without pleural effusions or endobronchial lesions and no pulmonary emboli (**Figure 3**). The patient had a gradual decline in the ejection fraction of his transplanted heart over years, with a two-dimensional echo on admission showing an ejection fraction of 45–50% and no major valve disease (unchanged from previous echo one year prior).

Management

In light of a borderline normal ejection fraction of 45–50%, which was stable over the last year, and only marginally elevated BNP on admission, neither graft dysfunction nor heart failure exacerbation was thought to be a significant contributor to the patient's illness. Additionally, the patient's vital signs (mild tachycardia thought to be from acute COVID-19 infection and borderline elevated blood pressure) pointed away from cardiogenic shock and need for mechanical circulatory

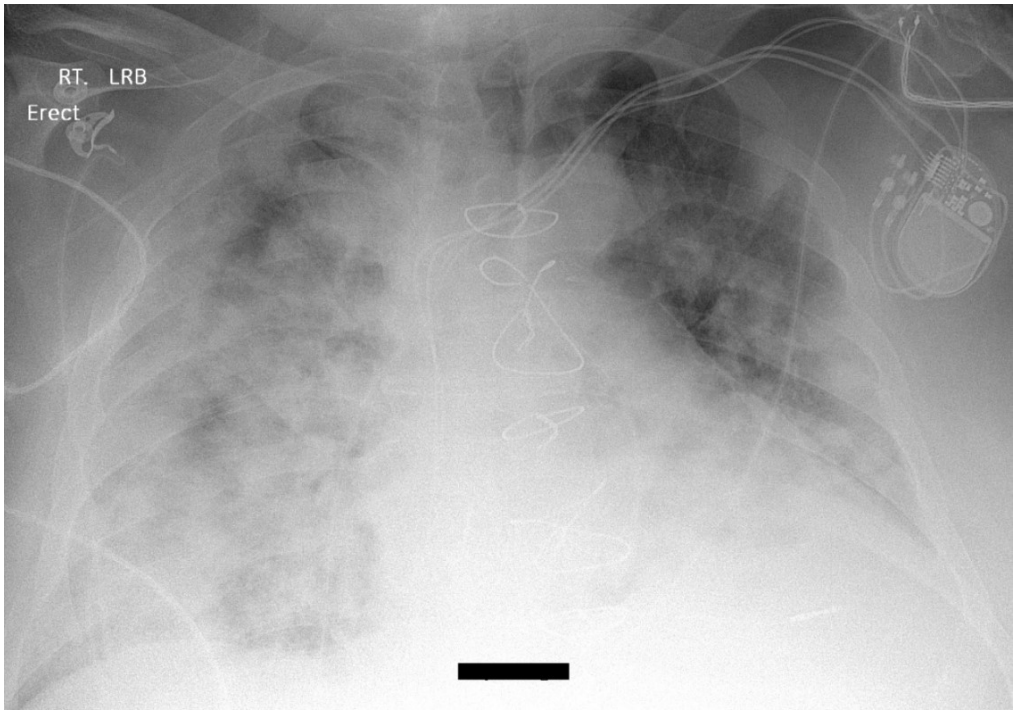

Figure 4. Repeat chest X-ray on day 5 showing new and worsening pulmonary edema and possible multifocal pneumonia.

support.

The patient was started on dexamethasone (6 mg IV daily) and remdesevir (200 mg as a single dose IV on day 1, followed by 100 mg IV daily) for acute hypoxic respiratory failure from COVID-19 pneumonia. All his immunosuppressive medications were continued on admission, and his tacrolimus dose was adjusted to maintain therapeutic serum levels. The patient's AKI improved with fluid resuscitation, and he was subsequently started on enoxaparin 0.5 mg/kg subcutaneous BID.

Serial chest X-rays showed new and worsening pulmonary edema and possible multifocal pneumonia (**Figure 4**). IV fluids were stopped, and the patient was diuresed using bumetanide (2 mg IV BID). The patient refused intubation and other advanced and invasive therapies, including renal replacement therapy. Inhaled epoprostenol was not tried in this patient as he presented in March 2021, when the role of inhaled prostacyclin analogues in COVID-19-associated acute respiratory distress syndrome (ARDS) was still being explored and there were no data on the mortality benefit of these drugs in COVID-19 patients, which is a subject of ongoing studies. Given active immunosuppression, the patient was started on broad-spectrum antibiotic coverage with linezolid (600 mg IV Q12H) and cefepime (2 g IV Q8H). Fungal cultures, including histoplasma and aspergillosis, were negative. The patient continued to develop progressive dyspnea with hypoxia. We decided to start treatment with tocilizumab (8 mg/kg IV single dose) for worsening COVID-19 pneumonia. IgG and IgM antibodies against SARS-CoV-2 were tested to check for immune response to the BNT162b vaccine and returned negative, suggesting absence of immunity against COVID-19 infection.

Follow-up

Over the course of 18 days, the patient's respiratory status significantly worsened despite being on a high flow nasal cannula with intermittent bilevel positive airway pressure (BiPAP). The patient again declined intubation, opting for comfort measures instead, and expired within a few hours.

Discussion

While the exact process of mRNA vaccine recognition by cellular sensors and the mechanism of sensor activation are still not clear [1], two kinds of RNA sensors—endosomal toll-like receptors and the RIG-I-like receptor family—have been identified. Tacrolimus inhibits calcineurin, which is involved in the production of interleukin-2, a molecule that promotes the development and proliferation of T-lymphocytes.[3] Mycophenolate depletes guanosine nucleotides preferentially in T- and B-lymphocytes and inhibits their proliferation, thereby suppressing cell-mediated immune

responses and antibody formation.[4] Both these drugs are an important part of the traditional maintenance immunosuppressive regimen for patients who undergo orthotopic heart transplant.[3, 5] While the efficacy of the COVID-19 vaccine in immunosuppressed patients continues to be studied, it is likely that suppression of cell-mediated immunity in transplant recipients impedes their ability to mount an appropriate immune response despite being able to detect the mRNA through intracellular RNA sensors, thereby limiting protection against COVID-19 infection in this population. There are reports of interleukin-6 inhibitors, such as clazakizumab, that have been successfully used to treat COVID-19 pneumonia in heart transplant recipients.[6] Our patient received tocilizumab, an interleukin-6 receptor antagonist, but unfortunately did not respond well to it, perhaps because of the severity of his illness and the extremely elevated level of interleukin-6 on admission, which is predictive of poor outcomes in COVID-19 infection.[7, 8] The use of convalescent plasma is no longer recommended by the COVID-19 Treatment Guidelines Panel [9]; however, data on its use in immunosuppressed patients are mixed.[9, 10]

Conclusions

We present a case of severe acute respiratory distress syndrome due to SARS-CoV-2 that developed in a heart transplant recipient on immunosuppression who had received two doses of an mRNA COVID-19 vaccine. Although the BNT162b vaccine is safe, data on its efficacy in transplant recipients are mixed. All immunocompromised patients should be encouraged to receive the booster dose of COVID-19 vaccine per CDC guidelines.[11] Further, the American Society of Transplantation and the International Society for Heart & Lung Transplantation jointly recommend third and fourth doses of the BNT162b vaccine in this patient population.[12] An early and aggressive treatment strategy should be considered in immunosuppressed patients with even mild or moderate COVID-19 infection, irrespective of vaccination status.

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