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Prolonged COVID-19 Positivity and Post-transplant Reactivation: A Diagnostic and Therapeutic Challenge

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Introduction

The COVID-19 pandemic has introduced significant challenges to transplant medicine, particularly in lung transplantation, where recipients are at increased risk for respiratory infections [1,2]. The virus's persistence in lung tissue has raised concerns about donor-derived transmission and reactivation in immunosuppressed patients [3]. Consequently, using COVID-19-positive donor lungs remains controversial.

Recent studies have shown no significant difference in early mortality or one-year survival between recipients of COVID-19-positive and -negative donor lungs, suggesting that carefully selected COVID-19-positive lungs may be safe for transplantation [4]. Furthermore, a case report demonstrated successful lung transplantation in a patient with persistently positive RT-PCR but high Cycle threshold (Ct) values and negative viral cultures, indicating that prolonged PCR positivity does not always reflect viable virus or active infection [5].

In this report, we present a unique case of SARS-CoV-2 reactivation following lung transplantation in a patient with persistently positive RT-PCR tests for four months and reassuringly high Ct values prior to transplant.

Case Report

A 57-year-old male with connective tissue disease-associated Interstitial Lung Disease (ILD) and chronic renal insufficiency was diagnosed with COVID-19 pneumonia in December 2023. He had received one dose of an adenovirus-based COVID-19 vaccine but developed a severe allergic reaction requiring mechanical ventilation and therefore received no further COVID-19 vaccinations. His ILD had been managed with immunosuppressants including rituximab, prednisone and mycophenolate mofetil.

After receiving dexamethasone and a brief course of remdesivir (discontinued due to abnormal liver function), the patient was discharged. However, by February 2024, he was re-hospitalized with acute hypoxic respiratory failure. Persistent RT-PCR positivity was noted and extensive evaluation revealed no alternative infectious source. Despite high-dose steroids, his condition did not improve, with an inability to wean from high flow nasal cannula. Given the lack of clinical improvement, the patient was listed for concomitant lung and kidney transplant.

Although RT-PCR remained positive for COVID-19, the transplant team proceeded, citing the prolonged interval since initial infection and a high Ct value of 30. The patient underwent Bilateral Orthotopic Lung Transplantation (BOLT) and subsequent kidney transplantation the following day. After initial complications, including reintubation for suspected primary graft dysfunction, he showed encouraging progress, weaning room air By Post-Operative Day (POD) 11 (Figure 1A).

On POD 16, the patient developed increasing hypoxia and bilateral pulmonary infiltrates on chest CT (Figure 1F). The patient was started on broad-spectrum antibiotics and subsequent bronchoscopy revealed no evidence of infection except for an ongoing positive RT-PCR for COVID-19. Given concerns for acute cellular rejection, the patient was treated with pulse dose steroids. Donor specific antibodies were negative. By POD 22, the patient required 50% FiO_2 *via* high flow nasal cannula. On POD 25, remdesivir was resumed and repeat cycle threshold sent, which returned at 24, a decrease from prior. By POD 27, the patient had significantly deteriorated, requiring Veno-Venous (VV) ECMO for refractory hypoxemia (Figure 1B). Due to uncertainty over the etiology of the patient's clinical decline, a lung biopsy was performed on POD 27. The biopsy revealed diffuse alveolar damage and parenchymal infiltrates consistent with SARS-CoV-2. PCR analysis confirmed the presence of SARS-CoV-2 in the lung tissue (Figure 1E).

Given concern for reactivation of COVID-19 infection, immunosuppression was reduced and he was treated with remdesivir and IVIG. With these therapies, the patient gradually recovered and was liberated from VV-ECMO. Unfortunately, the patient was left with a degree of pulmonary scarring from the insult and continues to require supplemental oxygen *via* nasal cannula (Figure 1C) (Figure 1).

Discussion

The authors believe that the decompensation post-transplantation observed in this case represents SARS-CoV-2 reactivation following lung transplantation in a patient with persistently positive RT-PCR testing and a high Ct. Although viral culture was not obtained, the absence of alternative etiologies, the patient's clinical response to antiviral therapy and demonstration of viral material on lung biopsy supports a diagnosis of COVID-19 reactivation as the primary driver of his post-transplant decompensation.

This finding contrasts with prior reports that suggested low risk of COVID-19 reactivation in similar clinical scenarios. We suspect the reason for reactivation in this case was failure to completely clear the virus due to

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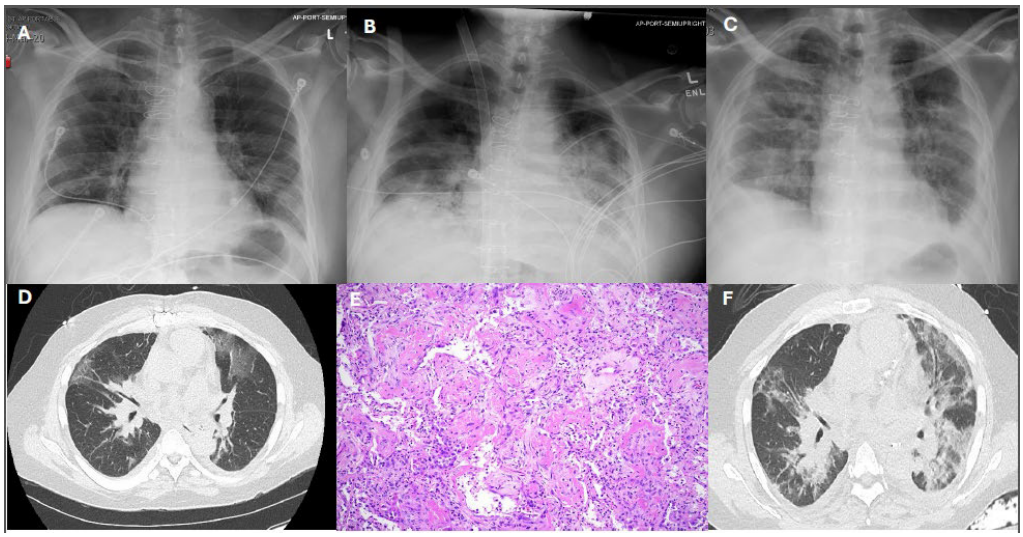

Figure 1. A) Chest radiograph on post-operative Day 11 showing clear lungs, **B)** Chest radiograph on post-operative Day 27 with bilateral lung infiltrates with right dual lumen internal jugular ECMO cannula, **C)** Chest radiograph post-operative Day 182 with residual bilateral infiltrates, **D)** CT scan post-operative Day 8 with minimal anterior ground glass opacities, **E)** Diffuse alveolar damage with hyaline membranes. (H&E, 200X) on lung biopsy and **F)** CT scan post-operative Day 16 with worsening bilateral infiltrates.

the profound immunosuppression used to treat the patient's CTD-ILD prior to transplant. Ultimately, this case emphasizes the need for caution in interpreting PCR results and highlights the potential for post-transplant complications in the setting of unresolved SARS-CoV-2 infection, particularly potential recipients on immunosuppression prior to transplantation.

Acknowledgement

None.

Conflict of Interest

None.

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