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## A Case Report of Breakthrough Infections With 2 SARS-CoV-2 Variants in a Lung Transplant Patient

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### ABSTRACT

A lung transplant (LT) patient developed 2 distinct episodes of COVID-19, confirmed by whole-genome sequencing, which was caused by the Delta, and then followed 6 weeks later, by the Omicron variant. The clinical course with Omicron was more severe, leading us to speculate that Omicron may not be any milder among LT patients. We discuss the potential mechanisms behind the Omicron not being any milder among LT patients and emphasize the need for outcomes data among these patients. Until such data become available, it may be prudent to maintain clinical equipoise as regards the relative virulence of the newer variants among LT patients.

### BACKGROUND

**T**HE B.1.1.529 (Omicron) variant has been reported to be associated with a milder form of COVID-19 in the general population. However, there is a lack of outcomes data among lung transplant (LT) patients infected with the Omicron variant compared to the earlier variants. We report an interesting case where a LT patient developed 2 distinct episodes of COVID-19 with B.1.617.2 (Delta) variant followed by the Omicron variant.

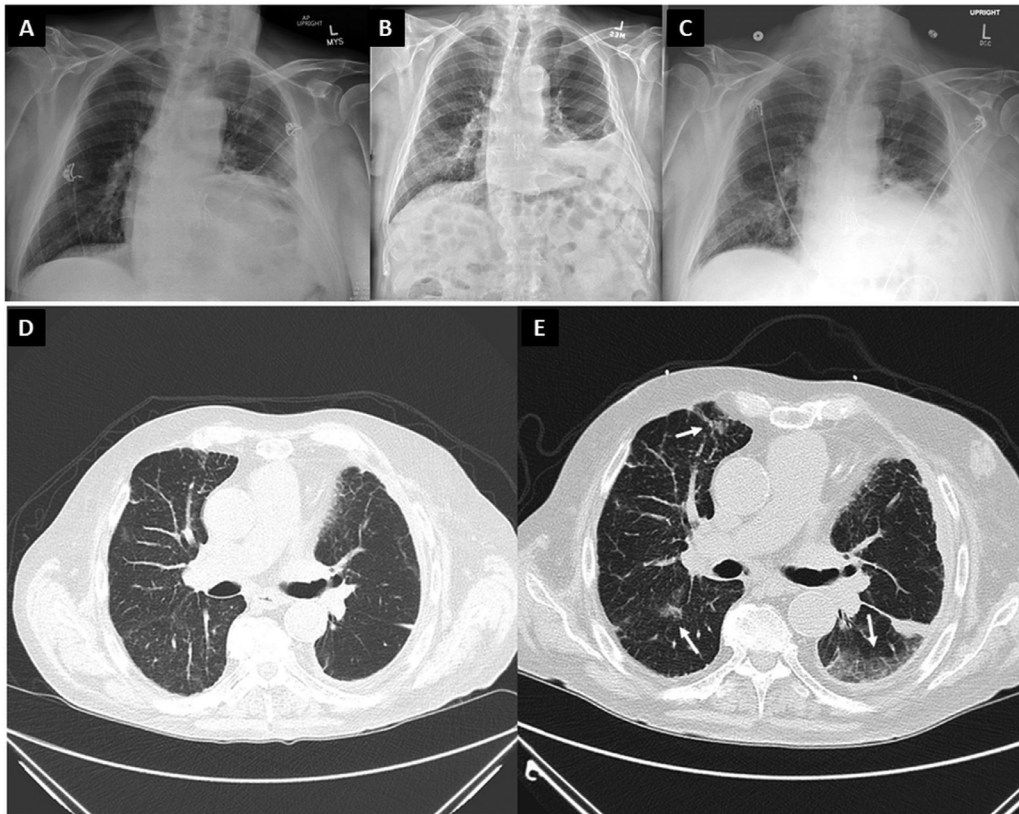
### CASE

Eight years ago, a 77-year-old man with bilateral LT for idiopathic pulmonary fibrosis, presented with a history of fever, cough, and malaise for 2 days. His past medical history was significant for candida tropicalis pericarditis needing pericardial wash, left hemidiaphragm paresis, Stage 4 chronic kidney disease, hepatic nodular regenerative hyperplasia with evidence of esophageal varices and portal hypertensive gastropathy, multiple skin cancers, and venous thromboembolic episodes requiring chronic anticoagulant use. He did not have any biopsy proven acute cellular or humoral rejection although he had been treated 3 times with pulse dose corticosteroids (methylprednisone 10 mg/Kg daily × 3 days) since his transplant. His immunosuppression regimen consisted of low dose prednisone (7.5 mg/day) and tacrolimus dose was maintained to target trough levels of 5-8 ng/mL. He had been on azathioprine early after

transplant followed by mycophenolate 2 years posttransplant. However, he was off either cell cycle inhibitors for 6 months because of recalcitrant skin cancers. The last laboratory tests before the infection revealed a total white blood cell count of  $7.1 \times 10^3/\text{mL}$  with an absolute lymphocyte count of  $1.4 \times 10^3/\text{mL}$  and Cylex Immuknow assay value of 441 ng/mL (with a low immune cell response defined as  $\leq 225$  ng/mL). He had good lung functions prior to the infection with forced expiratory volume in 1 second (FEV<sub>1</sub>) of 2.46 L (75% of predicted) and forced vital capacity of 3.08 L (70% of predicted). He had received 3 doses of BNT162b2 vaccine (Pfizer-BioNTech, BioNTech, Mainz, Germany) with the last dose 10 weeks ago.

A nasopharyngeal swab was positive for SARS-CoV-2 virus (real-time RT-PCR assay). The whole-genome sequencing revealed infection with the Delta variant. He was treated with intravenous casirivimab and imdevimab (600 mg each). Given the multiple comorbidities, he was admitted and started on remdesivir (200 mg IV once followed by 100 mg daily), along with prednisone burst (starting with 1 mg/Kg PO) per our institutional protocols. The inflammatory markers revealed mild

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**Fig 1.** Chest radiographs done at different time points. **(A)** Chest radiographs done at the time of diagnosis of the first episode of COVID-19 (confirmed as Delta variant). **(B)** Chest radiographs done at 4 weeks after diagnosis of the first episode of COVID-19. **(C)** Chest radiographs done at the time of diagnosis of the second episode of COVID-19 (confirmed as Omicron variant). **(D)** CT chest during the first episode of COVID-19 (confirmed as Delta variant). **(E)** CT chest during the second episode of COVID-19 (confirmed as Omicron variant).

elevation of C-reactive protein, lactate dehydrogenase, and D-dimer. Ferritin levels were normal, and chest imaging were unchanged from baseline (Fig 1A and Fig 1B). This was confirmed on a computed tomography chest which was also unchanged (Fig 1D). He had an uncomplicated course and was discharged home after completing 5 days of remdesivir. He returned to the clinic 4 weeks after the diagnosis feeling well with no significant change in spirometry (FEV<sub>1</sub> of 2.27 L, 69% of predicted and forced vital capacity of 2.98 L, 67% of predicted) from baseline.

However, 2 weeks later, he developed fever with cough again. This time he had noted a concurrent drop in his home lung functions and found to be hypoxic. Chest radiograph showed new bibasilar opacities (Fig 1C), and these were confirmed on a repeat computed tomography chest (Fig 1E). The nasopharyngeal swab was positive for the SARS-CoV-2 virus again. Given the clinical presentation and the emergence of the Omicron variant at the time, the patient was suspected to have a re-infection. The variant testing was positive for Omicron. All the laboratory markers were abnormal during this admission, with peaks and troughs that were more severe than previously (Fig 2). He remained symptomatic with respiratory failure necessitating an extension of the remdesivir to 10 days. He showed slow

improvement but remained with respiratory failure, necessitating discharge with home oxygen. He returned for the outpatient follow-up 4 weeks later and found to have a significant loss of lung functions (>20% decline in both FEV<sub>1</sub> [1.79 L] and forced vital capacity [2.32 L]) and persistent oxygen needs.

## DISCUSSION

With an extensive array of mutations on its spike protein [1], Omicron has demonstrated remarkable versatility in evading immunity. Indeed, in combination with significantly higher transmissibility, Omicron has fueled the highest surge in cases during the pandemic [2]. At the same time, the emergence of Omicron has been associated with milder illness leading to relative decoupling in the number of cases and deaths [3].

Our patient developed 2 episodes of COVID-19, 6 weeks apart, with the Delta confirmed as the initial variant followed by the Omicron variant. The short interval between the 2 infections meant that his immunosuppressive regimen, baseline comorbidities, and risk of severe disease as well as the available therapeutics, were similar during both infections. Furthermore, both infections occurred within 4 months since the last dose of the vaccine became protective. Finally, the patient's first episode of COVID-19 led to a



**Fig 2.** Line graph showing the trends in the inflammatory and laboratory markers during the 2 episodes of COVID-19. The blue shaded area represents the first COVID-19 episode from the Delta variant while the second episode from the Omicron variant is shaded red.

mild illness that did not require any potent immunosuppressives that may have had ill affects well beyond the acute illness. Given these features, the host factors can be deemed similar during both episodes of COVID-19, permitting a direct comparison of the severity of clinical disease from these 2 variants.

It is evident that the Omicron variant was associated with a more severe clinical course in this patient. This encompassed the severity of symptoms at presentation, development of COVID pneumonia, new-onset respiratory failure, worse laboratory abnormalities (Fig 3), longer hospital stay, and finally, significant loss of lung functions. This occurred despite the patient being vaccinated with 3 doses of the mRNA vaccine and the recent recovery from the Delta variant.

The course of illness from Delta was expectedly mild, a variant against that the mRNA vaccines appear to be effective in attenuating the severity of the disease [4]. One of the noteworthy differences in the therapeutic strategy pertains to the use of monoclonal antibodies during the first episode. And while this may have favorably altered the subsequent clinical course of the Delta infection, it does not explain the significant difference in clinical presentation. Despite a similar duration of symptoms (2 days), the Omicron episode led to severe disease at diagnosis.

The higher severity of illness with Omicron with similar host factors is unexpected. A large body of epidemiologic data has found that despite increased transmissibility and efficient immune evasion, Omicron is associated with a milder illness with a lower risk of severe illness, hospitalization, and death [2,5,6]. The increased transmissibility has been ascribed to a significantly higher replication competence of the Omicron in the airways than the Delta or the wild-type virus [7]. On the other hand, Omicron has a lower replication competence in the lung parenchyma [8], and viral loads in the ex-vivo lung cell cultures infected with Omicron are lower than those with other variants. While the cellular tropism of Omicron reduces the risk of pulmonary involvement, the direct infection of pulmonary parenchyma may not be the sole mechanism of severe disease. There is extensive evidence linking the innate immune response activation as one of the key manifestations of COVID-19 [9]. Depending on the extent of the viral load in the airways, the local activation of innate immune responses is followed by a systemic activation early in the course of illness. These responses combined with a balanced cytokine response limits the ongoing viral replication in an immunocompetent patient [10]. However, among LT patients, a profound activation of the innate immune system can cause significant allograft dysfunction [11] as a direct effect or via the bystander activation of alloimmune pathways [12]. In this regard, patients with LT are uniquely vulnerable to the adverse effects of COVID-19 due to the allograft itself being the target of the virus. With a significant propensity for immune evasion and achievement of higher viral loads in the airway, Omicron may be associated with a similar or even more severe involvement of the allograft among LT patients.

Given such concerns, it may be prudent to avoid generalizing the clinical outcomes after Omicron infection among the general population to LT patients. We recommend that LT patients be counseled regarding the potential risk of significant allograft injury despite the lower virulence of the newer variants and

recommend adherence to multipronged infection prevention and risk mitigation strategies.

#### DATA AVAILABILITY

Data will be made available on request.

#### DISCLOSURES

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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