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Atypical Unilateral SARS-CoV-2 Pneumonia in a Single Lung Re-Transplanted Patient: A Case Report

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ABSTRACT

Background. Since December 2019, the SARS-CoV-2 pandemic significantly has impacted the medical community. When infected with SARS-CoV-2, most of the patients developed bilateral pneumonia. We have herein presented the atypical case of a patient who developed unilateral SARS-CoV-2 pneumonia, affecting only the second lung allograft re-transplanted (re-LTX).

Case Presentation. A SARS-CoV-2 infection occurred in a 2-dose vaccinated patient with LTx with a history of second unilateral lung transplantation performed after an end-stage bronchiolitis obliterans syndrome. The first symptoms started with a flu-like syndrome, and the patient's clinical condition worsened with nonsevere acute respiratory failure requiring conventional oxygen therapy. Treatment consisted in administrating specific anti-SARS-CoV-2 monoclonal antibodies along with probabilistic antibiotherapy, anticoagulation, and steroids. On day 7, the patient was discharged from hospital. We aimed to assess this atypical unilateral pneumonia based on different explorations. A ventilation scintigraphy showed a severe ventilation decrease owing to end-stage bronchiolitis obliterans syndrome within the left first allograft, which may be associated with asymmetrical virus diffusion between the 2 lungs. We did not identify any other relevant differences with respect to the 2 donors' clinical characteristics. Using specific immunohistochemistry staining against angiotensin converting enzyme-2 receptor, the main known receptor for SARS-CoV-2 binding on airway epithelial cells, no staining difference was observed between the 2 lung biopsies that were collected at re-LTx from each lung.

Conclusions. With the present case report, we aimed to highlight how this kind of unusual presentation may be caused by the difference of ventilation between the 2 lungs.

SINCE December 2019, the COVID-19 worldwide pandemic has been a major concern for the medical community. In January 2022, more than 306 million cases were documented around the world, including 5.5 million deaths (World Health Organization website: https://covid19.who.int/; John Hopkins University website: https://coronavirus.jhu.edu/). Yet, there is insufficient understanding about SARS-CoV-2 infection pathophysiology [1]. Angiotensin-converting enzyme 2 (ACE2) has been identified as the receptor used by SARS-CoV-2 for its entry into host cells, using its spike glycoprotein [2,3], especially in the lower respiratory tract while targeting alveolar type 2 cells [4].

The impact of the COVID-19 pandemic on solid organ transplant recipients, especially concerning patients with lung transplant (LTx), resulted in only a limited number of studies even though both disease severity and prognosis turn out to be worse in this patient population owing to immunosuppression (25%-35% mortality) [5−7]. In June 2021, 204 patients with LTx developed an infection secondary to SARS-CoV-2 (6.7%) in France, with 32 deaths reported (15.2%) in this population since the beginning of the pandemic [8].

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In most cases of COVID-19 pneumonia occurring in LTx patients reported to date through case reports or series, both lungs were affected, with bilateral lung infiltrates described. A monocentric case series study described dissimilar findings revealed on chest x-ray performed in patients with a single lung transplantation, with 17% of them having infiltrates on the graft side only, vs 4% with infiltrates on the native side only [6]. Moreover, in a Spanish case report, the authors reported COVID-19 pneumonia affecting only the native lung in a patient with single lung transplantation [9]. It also must be mentioned that infiltrates may not be visible in the native lung because of very severe parenchymal fibrosis or emphysema within the native diseased lung.

We have presented herein the case of a patient who underwent single lung transplantation 18 months earlier because of terminal chronic lung allograft dysfunction after a first bilateral LTx for chronic obstructive pulmonary disease; this patient developed unilateral SARS-CoV-2 pneumonia affecting only the second lung allograft transplanted on re-LTx.

CASE PRESENTATION

The clinical course is summarized in Fig 1A. In November 2016, this 68-year-old man underwent a first bilateral LTx for chronic obstructive pulmonary disease. Three years later, a significant drop in forced expiratory volume in the first second occurred, associated with eosinophilia and humoral chronic rejection, persisting despite optimal treatment. Several chest computed tomography (CT) scans revealed pictures of bilateral air trapping, thereby confirming the diagnosis of chronic lung allograft dysfunction, with a bronchiolitis obliterans syndrome (BOS) phenotype. In February 2020, a right single lung re-LTx was performed. A lung biopsy from the explanted right lung allograft and another one from the second donor's left lung, the latter being not used during the procedure, were collected. The patient's maintenance immunosuppression treatment consisted of tacrolimus (1.7 mg twice daily), mycophenolate mofetil (1000 mg twice daily), and prednisolone (10 mg/d).

As a prophylaxis of COVID-19, the patient received a first vaccine shot of mRNA-1273 (Moderna) in January 2021, followed by a BNT162b2 (Pfizer-BioNTech) vaccine dose 4 weeks later.

Fourteen months after the second LTx, on April 14, 2021, a nasopharyngeal swab using reverse transcription polymerase chain reaction (RT-PCR) was performed after the patient reported a known COVID-19 exposure, while being tested positive for SARS-CoV-2 variant under investigation - United Kingdom variant, with the patient asymptomatic at that time. The first symptoms started on April 17, 2021, with a flu-like syndrome including fever (39°C), asthenia, myalgia, anorexia, vomiting, diarrhea, and ageusia. A few days later, on April 21, 2021, his clinical condition worsened with oxygen saturation at 90% under F_IO_2 21%. The patient was then hospitalized in our respiratory department. A nonsevere acute respiratory failure was observed requiring conventional oxygen therapy at 2 L/min. A low-dose chest CT scan that was performed at admission revealed patchy ground glass opacities that were consistent with moderate COVID-19 pneumonia; yet affecting the right lung only (Fig 1B). Laboratory tests exhibited an acute kidney injury with

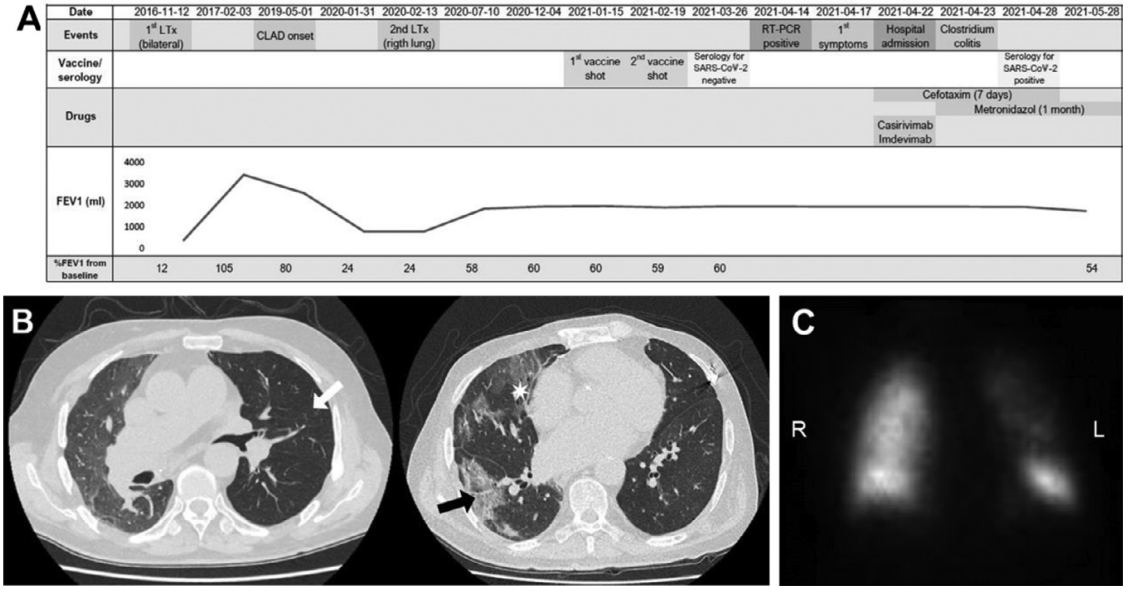

Fig 1. (A) The patient's clinical characteristics and main events recorded since the first lung transplantation (LTx) and on SARS-CoV-2 pneumonia. **(B)** Pulmonary computed tomography showing patchy areas of consolidation (black arrow) and ground-glass opacities (white star) secondary to COVID-19 pneumonia in the right lung only, and BOS air trapping (white arrow) consequence in the left lung. **(C)** Lung ventilation scintigraphy showing a major asymmetric ventilation between the lungs. BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; FEV1, forced expiratory volume in the first second; LTx, lung transplantation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

creatinine enzyme at 132 μmol/L (64-104 μmol/L) and urea at 15.7 mmol/L (2.5-7 mmol/L), along with a severe inflammatory syndrome with a creatine reactive protein level at 124 mmol/L (<4 mg/L). We observed an eosinopenia at 0.0 G/L (0.05-0.8 G/L) and lymphopenia at 0.69 G/L (1-4 G/L). A previous specific serology for SARS-CoV-2 (anti-spike and anti-nucleocapsid IgG) tested negative on March 26, 2021, after the first 2 vaccine shots, whereas serology turned out positive at admission on April 23, 2021 (anti-spike IgG >80 000 AU/mL for a positivity threshold >50 AU/mL using Abbott IgG II anti-SARS-CoV-2 assay). The patient was treated using a specific anti-SARS-CoV-2 monoclonal antibody association (casirivimab and imdevimad), which was initiated the second day of his hospital stay, meaning 5 days after symptom onset. We conducted a probabilistic antibiotic therapy using cefotaxim for 7 days and preventive anticoagulation with enoxaparin. The management of maintenance immunosuppressive treatment consisted of suspending mycophenolate mofetil and increasing steroid dosing to 1 mg/kg, which was followed by progressively decreasing dosing back to his current dose. During hospitalization, a Clostridium difficile colitis was diagnosed, possibly caused by emprical antibiotic therapy, and was treated with metronidazole for 1 month. On day 7, the patient was stable with partial recovery and discharged from hospital.

Two months later, a significant drop in forced expiratory volume in the first second (1720 mL vs 1960 mL), as well as eosinophilia in blood samples, were noticed. Owing to the high risk of acute rejection possibly occurring after such a severe infection, a bronchoscopy and biopsies were performed in August 2021. The transbronchial biopsies did not show any signs of rejection. Eight months after the SARS-CoV 2 pneumonia, eosinophilia counts in blood samples were still increased (0.85 G/L), whereas lung function had returned to baseline values.

DISCUSSION AND CONCLUSIONS

This is an original case reporting a nontypical form of COVID-19 pneumonia that only affected the second lung allograft, whereas no signs of infection were observed in the first allograft, which only exhibited some air trapping secondary to the BOS. Thus, we sought to further understand why COVID-19 −related opacities could only be seen in the right lung. Written informed consent was obtained from the patient before using his medical record and data information. A first reason may come from severe air trapping resulting from end-stage BOS while inducing disparities in ventilation within the left lung, which may be associated with asymmetrical virus diffusion between the 2 lungs. This could explain the radiological patterns of infection only visible in the best ventilated lung. To validate this assumption, the patient was invited to undergo a ventilation/perfusion scintigraphy (Fig 1C), confirming better ventilation within the right lung.

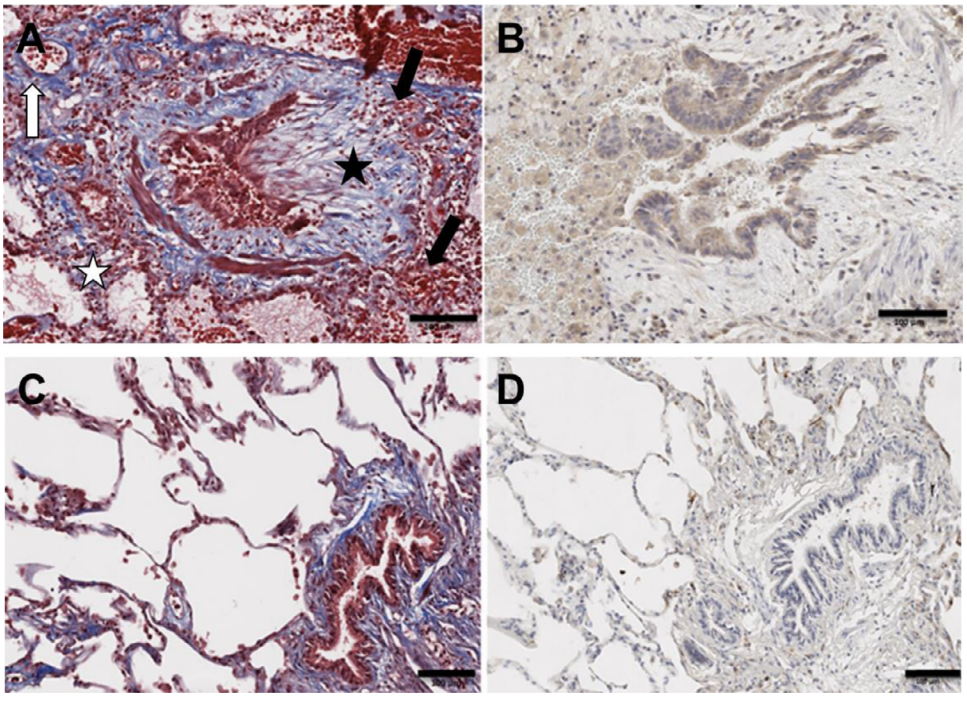

Fig 2. Optical examination of FFPE lung samples and analysis in immunohistochemistry. FFPE lung tissue samples collected from the right first lung allograft, affected with BOS **(A), (B)** and from the second donor left lung (collected at the time of the right single retransplantation) **(C), (D)**. Masson's trichrome staining **(A), (C)** and anti-ACE2 staining **(B), (D)** are shown on this figure. Some airways from the first lung allograft **(A), (B)** showed specific lesions of obliterans bronchiolitis (black star), characteristic of BOS, associated with peri-airway (black arrows) and vessel inflammation (white arrow), alveolar damage (white star), and sclerosis. Scale bar: 100 μm. ACE2, angiotensin-converting-enzyme-2; BOS, bronchiolitis obliterans syndrome; FFPE, Formalin-Fixed Paraffin-Embedded; LTx, lung transplantation.

Another hypothesis may be that the left lung parenchyma was too damaged to develop COVID-19−related ground glass opacities. Nevertheless, this assumption is unlikely to be relevant in this case. Indeed, as only the left lung parenchyma was affected by BOS, no specific injuries like emphysema or fibrosis could have prevented an optimal evaluation of radiological findings.

Another reason to explain this atypical clinical presentation may be that the patient displayed lungs from 2 different donors, with their own characteristics. However, we did not find any clinical difference between the 2 donors. Fig. 2.

Next, we sought to assess whether ACE2 expression differed between the lungs from the 2 donors. Several studies demonstrated that certain clinical conditions were likely to influence ACE2 expression and SARS-CoV-2 pathophysiology [10]. To better understand this purpose, we employed the lung tissue biopsies collected at the time of re-LTx, before the present infectious episode, from the right first explant (first donor) and from the second left donor's lung, which was not used for LTx, providing us with good representative tissue samples of the patient's both transplanted lungs. Specific immunohistochemistry anti-ACE2 staining was performed (Mouse monoclonal, MAB933, R&D Systems, Minneapolis, MN, United States). As a positive control for anti-ACE2 staining, kidney tissue was employed, with Masson's trichrome staining performed, as well. Concerning our positive control, ACE2 was strongly expressed only within the renal tubules, yet not within the glomerulus. With respect to the right lung explant (Fig 2A), some airways showed specific lesions of obliterans bronchiolitis, characteristic of BOS, associated with peri-airway and vessel inflammation, alveolar damage, and sclerosis. In the donor's left lung, which was considered a normal lung, no significant histologic lesions were observed (Fig 2C). No significant difference of anti-ACE2 staining was observed within the bronchial or alveolar epithelium in both lung samples (Fig 2B, D).

This nontypical presentation of the disease did not seem to influence its severity or the clinical evolution in our case. Unilateral SARS-CoV-2 pneumonia was described to occur in 15% patients affected by COVID-19 in a large systematic review published by Adams et al [11]. With the present case report, we aimed to highlight how this kind of unusual presentation may be caused by the difference of ventilation between the 2 lungs.

This case report displays several limitations that we would like to mention. First, as this is a single clinical case, no pathophysiological considerations should be extrapolated from this report. As we did not observe any difference in ACE2 expression between the 2 lung biopsies, it could be assumed that there possibly was a lack of tissue representativity to highlight such a difference, with only one biopsy available per lung, given that a previous case study demonstrated that only a few alveolar cells exhibited ACE2 receptors [4]. Moreover, immunohistochemistry staining used in our study may not be the only strategy to explore specific ACE2 expression variations. Ortiz Bezara et al [4] used RNA sequencing and immunofluorescence staining, with ACE2 receptor mRNA expression assessed using quantitative RT-PCR in a study including type 2 diabetes patients [10].

We have herein presented an original case of an atypical and unilateral SARS-CoV-2 pneumoniae in a patient having undergone single re-LTx, which was probably the consequence of end-stage BOS-related ventilation asymmetry. Similarly to many patients infected by COVID-19, including patients with LTx, the diagnostic was based on the context of known COVID-19 exposure, the presence of typical symptoms, the positivity of the nasopharyngeal swab using RT-PCR, and the typical opacities observed on chest CT scan. With our study using lung biopsies collected at the time of second LTx before this episode of COVID-19 infection, we aimed to look for risk factors for developing a COVID-19 infection and specific pathologic differences between the 2 lungs allografts. All the pathologic features described on the lung biopsies (lesions of obliterans bronchiolitis, peri-airway and vessel inflammation, alveolar damage, and sclerosis) were consecutive to post-LTx complications only, and not related to the COVID-19 pneumonia. This further stresses the need to acquire new data with respect to LTx patient management. Cohort studies and prospective trials should be instrumental in providing prompt answers to these new issues.

DATA AVAILABILITY

Data will be made available on request.

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Written informed consent was obtained from the patient prior to using his medical record and data information for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. According to French law (loi Jardé), institutional review board approval was not required. All methods were performed in accordance with the relevant guidelines and regulations as stated in the Declarations of Helsinki. The authors declare that they have no competing interests.

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