



Acute exacerbation of post-COVID-19 pulmonary fibrosis: air travel as a potential trigger

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TO THE EDITOR,

Pneumonia secondary to coronavirus disease 19 (COVID-19) has been the leading cause of hospitalization and death in affected patients during the ongoing pandemic, mainly due to acute hypoxemic respiratory failure. However, to date, long-term follow-up data from the increasing number of recovered patients, especially those with severe disease and mechanical ventilation requirements, remain scarce.⁽¹⁾ Persistent physiological impairment⁽²⁾ and even late response to corticosteroid treatment for post-COVID-19 interstitial lung disease (ILD) have been described, particularly in the context suggestive of the presence of organizing pneumonia (OP).^(1,3)

Acute exacerbation (AE) of ILD was initially reported for idiopathic pulmonary fibrosis (IPF) and is currently best defined as an acute worsening or development of dyspnea, associated with new bilateral ground-glass opacities (GGO) and/or consolidations superimposed in a pattern consistent with usual interstitial pneumonia (UIP), not fully explained by cardiac failure or fluid overload, in patients with a previous or concurrent diagnosis of IPF.⁽⁴⁾ AE has been described in ILDs other than IPF and is often associated with a poor prognosis.⁽⁵⁾

Herein, we describe the case of a 68-year-old male admitted to our hospital due to COVID-19 (confirmed by RT-PCR from nasal swab), who presented dyspnea and became hypoxemic twelve days after the onset of symptoms. His comorbidities included mild hypertension, dyslipidemia, and coronary artery disease. He had no history of respiratory disease, and a CT scan of the chest performed a few days after symptom onset revealed only sparse GGO, with no sign of chronic lung disease (Figures 1A and 1D).

The patient required progressively increasing respiratory support, initially through a nasal cannula, then high-flow oxygen cannula (HFNC) and non-invasive ventilation, and, finally, invasive mechanical ventilation (MV). The lung-protective ventilation strategy was assured throughout treatment, a cycle of prone positioning was needed, and estimated respiratory system static compliance was 20 mL/cmH₂O. After eight days, the patient was completely weaned from MV and successfully extubated but still required oxygen treatment with HFNC for 11 days due to persistent hypoxemia. Motor rehabilitation was initiated for critical illness polyneuropathy and resting hypoxemia, with the need for low-flow nasal cannula

support; a persistence of accentuated exercise-induced desaturation was observed. Oxygen requirements slowly and progressively decreased, and around one month after extubation, he remained on room air at rest, with mild desaturation during exercise.

A CT scan of the chest, performed two months after symptom onset, showed persistent GGO with predominantly peripheral distribution in the upper lobes, in addition to reticulation, GGO, traction bronchiectasis, and areas of architectural distortion in the lower lobes, suggesting the presence of post-COVID-19 pulmonary fibrosis (Figures 1B and 1E). Corticosteroid treatment was used throughout hospitalization, with a slow taper regimen, due to persistent physiological impairment and a presumed benefit from extended regimens.⁽⁶⁾ At discharge, approximately 75 days after hospitalization, the patient seemed better, tolerating exercises in the rehabilitation center with small oxygen requirements and a peripheral oxyhemoglobin saturation of 93% on room air. The patient traveled by plane back to his hometown, with instructions for supplemental oxygen usage during the flight.

The flight lasted two hours and was otherwise uneventful, except for increasing oxygen requirements. Upon arrival, increasing dyspnea and oxygen requirements at rest were noted. Twelve hours after arrival, the patient was readmitted to the hospital due to worsening dyspnea and hypoxemia. Laboratory tests demonstrated only a mild elevation of serum C-Reactive Protein and leukocytes. Pulmonary embolism and cardiac fluid overload were ruled out. A CT scan of the chest showed new diffuse GGO and consolidations (Figures 1C and 1F). A molecular panel of respiratory viruses was negative, except for persistent SARS-CoV-2 RNA detection. Blood and sputum cultures were negative. Empirical broad-spectrum antibiotics and high-dose corticosteroid treatment (approximately 2 mg/kg) were initiated, and the patient was again placed on HFNC oxygen support. Symptoms and hypoxemia resolved around three weeks later, and the patient was discharged with a recommendation of avoiding immediate air travel.

Post-COVID-19 ILD remains poorly understood, and the time of follow-up to determine the presence of irreversible changes without lung sampling has not yet been established. Nonetheless, many patients will present persistent CT abnormalities at 6-months of follow-up, and gas exchange impairment seems to be the most common

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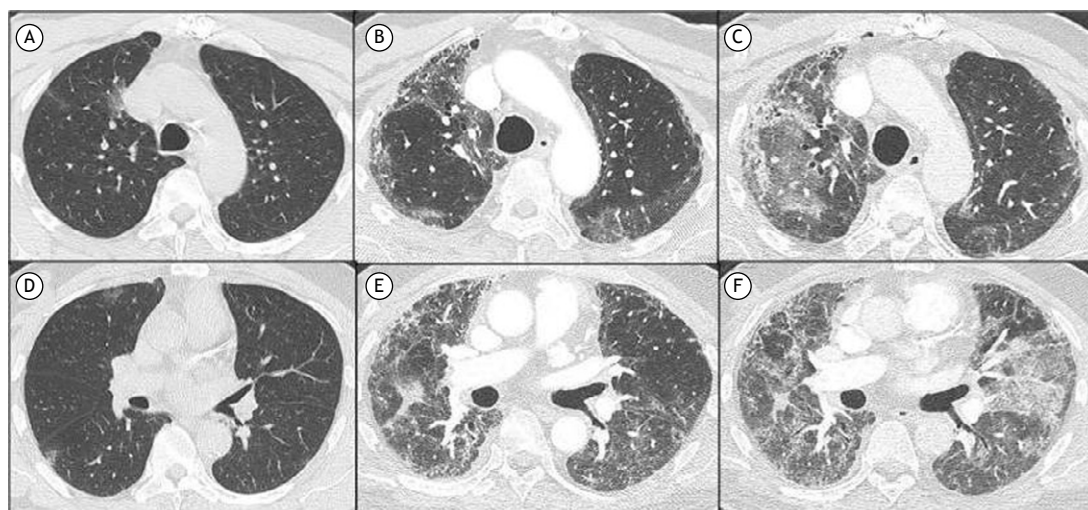


Figure 1. Chest CT scans demonstrating mild ground-glass opacities (GGO) and otherwise preserved lung parenchyma a few days after symptom onset (A and D); persistent peripheral GGO in the upper lobes and GGO, reticulation, and traction bronchiectasis in the lower lobes two months after symptom onset (B and E); new GGO and consolidations superimposed to the previous pattern on readmission (C and F).

physiological outcome; both may be related to initial disease severity.⁽⁴⁾ Age, gender, the need for high-flow oxygen support and mechanical ventilation, and the extent and severity of lung involvement increase our patient's risk of developing pulmonary fibrosis as a long-term sequela of COVID-19.

AE-IPF and ARDS share many common pathophysiological features, including the overexpression of proinflammatory cytokines and histological patterns of diffuse alveolar damage, with clearly overlapping clinical-radiological criteria.⁽⁷⁾ The AE of ILD was extensively reported and is currently classified as triggered by specific events, including infection, drug toxicity, and aspiration, or idiopathic, when no identifiable cause is present.^(4,5) However, therapeutic interventions for AE have not been completely defined.

To our knowledge, AE in patients with post-COVID-19 ILD had not been previously reported, according to a review performed on May 13, 2021, searching the MEDLINE and Web of Science databases. Although the possibility of reinfection by COVID-19 cannot be completely ruled out as the etiology, we consider such a hypothesis unlikely based on the very short time from symptom onset to respiratory deterioration.

Migratory pulmonary infiltrates characterizing OP have been described in COVID-19 patients,⁽⁸⁾ including delayed presentations,⁽⁹⁾ particularly associated with hematologic malignancies.^(8,9) However, lung infiltrates were acutely superimposed to persistent changes (seen throughout disease progression), rather than migratory, in our patient.

Additionally, air travel has been anecdotally reported as a potential trigger for AE-IPF, with presumed mechanisms of hypobaric-hypoxia inflammation and the recurrent mechanical stretching of the lungs.⁽¹⁰⁾ Our patient received supplemental oxygen during the whole flight, although oxygen requirements increased during travel. Air travel for patients with lung diseases is generally deemed safe, although mild to moderate symptoms, including worsening dyspnea, seem to be very common,⁽¹¹⁾ and these patients are usually not followed up once they reach their destiny.

The number of patients with post-COVID-19 fibrosis will probably increase in the upcoming years, as COVID-19 has affected a large population around the world and is still ongoing. Further studies are warranted to answer two major questions raised by this report: 1- may post-COVID-19 fibrosis be marked by acute respiratory worsening, characterizing AE, similar to other fibrosing ILDs? 2- could air travel be a potential trigger of AE in ILDs?

AUTHOR CONTRIBUTIONS

AFA: study design, data collection, and writing and reviewing the manuscript. JMS: writing and reviewing the manuscript. RKF: writing and reviewing the manuscript. OGRN: data collection and writing and reviewing the manuscript. CRRC: writing and reviewing the manuscript. BGB: study design, data collection, and writing and reviewing the manuscript.

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