J Bras Pneumol. 2023;49(1):e20220330
https://dx.doi.org/10.36416/1806-3756/e20220330

COVID-19 and pulmonary alveolar proteinosis: an unusual combination

Philippe de Figueiredo Braga Colares[1], Natalia Fernandes da Silva[1], Ronaldo Adib Kairalla[1], Bruno Guedes Baldi[1]

TO THE EDITOR:

Pulmonary alveolar proteinosis (PAP) is a rare entity characterized by the alveolar accumulation of lipoproteins, secondary to macrophage dysfunction, which leads to impaired surfactant clearance. According to the pathogenetic mechanism and responsible etiology, the disease may be classified into three distinct groups: primary (autoimmune or hereditary), secondary, and congenital.[1,2] Additionally, all etiologies are associated with the deregulation of activation and differentiation of lung defense cells, mainly alveolar macrophages, resulting in a greater predisposition to the development of opportunistic lung infections. In recent years, COVID-19 has become the leading cause of respiratory failure worldwide, with a potential to determine worse outcomes in patients with previous lung disease.[3]

An international multicenter study[4] showed that patients with interstitial lung disease are at an increased risk of death from COVID-19, when compared with patients with no interstitial lung disease or other chronic lung disease (overall mortality was 49% and 35%, respectively; p = 0.013), particularly those with poor lung function (FVC < 80% of predicted) and obesity. However, there are few data regarding COVID-19 and rare lung diseases. Recent series[5,6] in patients with lymphangioleiomyomatosis and PAP showed increased rates of hospitalization in these populations (approximately one-third of these patients in both studies).

Although we were unable to quantify anti-GM-CSF antibodies, given the absence of an underlying disorder causing secondary PAP (hematologic diseases, immune defects, or inhalational exposures), we report herein the cases of two patients with presumable autoimmune PAP and COVID-19. The first patient was a 46-year-old woman with stable PAP, diagnosed nine years before, who underwent whole lung lavage (WLL) four years before. After WLL, basal SpO_2 remained stable at 95% on room air. She was admitted to the emergency unit with a complaint of dyspnea for one week, fever (38°C), tachycardia, and SpO_2 = 80% on room air. Chest CT scans, when compared with those taken five months before, showed an increase in the extent of bilateral diffuse ground-glass opacities with inter- and intralobular septal thickening that were compatible with the crazy-paving pattern (Figures 1A and 1B). Nasopharyngeal PCR for SARS-CoV-2 was positive. The patient was initially treated with methylprednisolone (1 mg/kg per day), ceftriaxone plus azithromycin, and supplemental oxygen via nasal cannula. After one week, she had partial clinical improvement, but persisted with SpO_2 = 83-85% on room air. Then, a WLL was initially performed on the left lung with the infusion of 30 liters of 0.9% saline at 37°C, and the patient was subsequently referred to the ICU. Two weeks later, the same procedure was performed on the right lung. After one week, she presented progressive clinical improvement, and SpO_2 was 92% on room air. She was discharged after 49 days of hospitalization. Chest CT scans at discharge demonstrated a significant reduction in the extent of pulmonary opacities (Figure 1C).

The second patient was a 48-year-old man, diagnosed with PAP five years before, who underwent one WLL three years before. He was admitted to the emergency unit complaining of odynophagia and fever for 5 days, subsequently evolving to dyspnea and dry cough. SpO_2 was 88% on room air and PCR for SARS-CoV-2 was positive. Six months before, he was stable, and SpO_2 was 95% on room air. CT scans, when compared with those taken nine months before, demonstrated an increase in the extent of bilateral diffuse ground-glass opacities with thickening of the inter- and intralobular septa, confirming the identification of the crazy-paving pattern (Figures 1D and 1E). He was initially treated with supplemental oxygen via nasal cannula and methylprednisolone (1 mg/kg per day). The patient presented with significant clinical improvement and was discharged 10 days after hospitalization (SpO_2 = 93% on room air). However, he needed supplemental oxygen to perform his daily activities and has been under follow-up in the outpatient clinic, repeating the chest CT two months after discharge (Figure 1F).

Few studies described the combination of PAP and COVID-19, and none, to the best of our knowledge, described the performance of WLL in patients with both diseases. A recent European multicenter study[6] described the incidence and outcomes of patients with PAP coinfected with COVID-19. Despite having similar COVID-19 rates when compared with the general population (about 15%), patients with PAP had a higher risk of hospitalization and death (35% required hospitalization, almost 50% of those in the ICU, and, of these, 27% died or underwent lung transplantation). Treatment with inhaled GM-CSF was discontinued in all patients, and no patient underwent WLL during hospitalization.[6]

Some studies have evaluated the relationship between COVID-19 and the role of GM-CSF.[7] In the early stages of infection, the role of GM-CSF may be protective as it would help limit virus-related lesions. However, in the later stages of COVID-19, inadequate release of several cytokines (cytokine storm), including IL-6 and GM-CSF, predisposes to inflammatory lung injury, and, finally, to ARDS.[7]

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), Brasil.

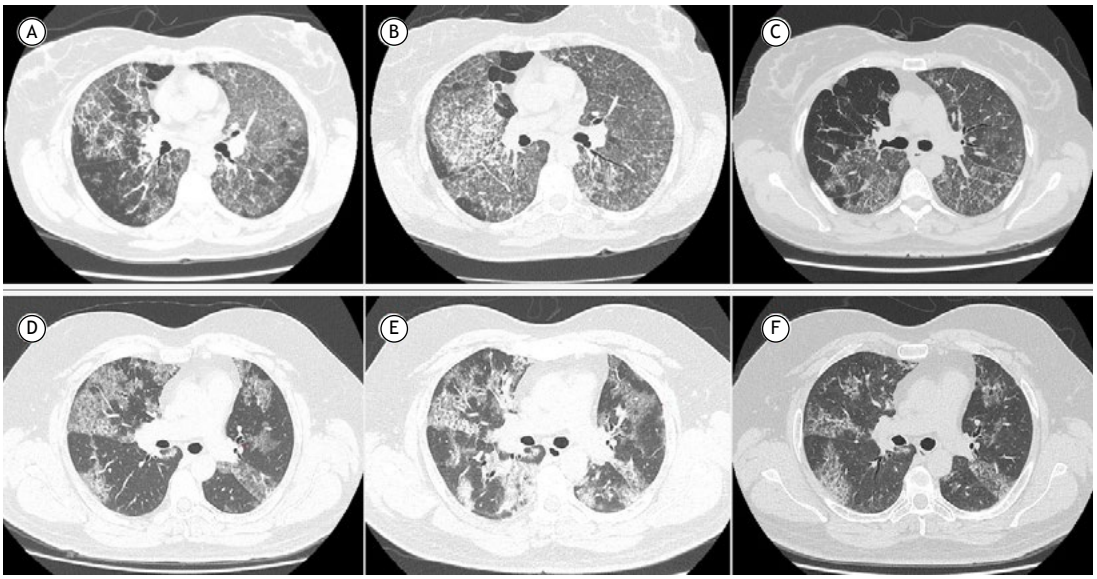

Figure 1. Chest CT scans showing bilateral and diffuse ground-glass opacities with inter- and intralobular septal thickening (crazy-paving pattern). Chest CT scans of a 46-year-old female patient taken five months before the COVID-19 infection (in A); during the COVID-19 infection (in B), showing an increase in the extent of lesions; and after whole lung lavage (in C). Chest CT scans of a 48-year-old male patient taken nine months before the COVID-19 infection (in D); during the COVID-19 infection (in E), showing an increase in opacities and appearance of new lesions; and two months after discharge (in F).

Management of PAP depends on its etiology and severity, and aims to relieve symptoms, improve oxygenation, and improve the quality of life of patients. Asymptomatic patients or those with mild symptoms do not require immediate treatment and can be followed with periodic reassessment. However, in patients with moderate to severe disease and progressive respiratory failure, the gold standard treatment is WLL.[1,2] In patients with autoimmune PAP, an association with experimental therapies, such as (subcutaneous or inhaled) recombinant GM-CSF, rituximab, or plasmapheresis may be performed. In selected, refractory cases, lung transplantation may be an option.[8]

It is also noteworthy that the two cases reported here had stable disease for years and were hospitalized with significant worsening of respiratory symptoms, hypoxemia, and an increase in the extent of tomographic opacities, probably secondary to COVID-19. Furthermore, the imaging findings were insufficient to differentiate between worsening of PAP and COVID-19. Neither received GM-CSF therapy, since this is unavailable in our center; however, one patient underwent WLL, which was indicated by the presence of persistent hypoxemia.

In conclusion, it is yet to be known whether the clinical and tomographic worsening observed in these two patients was related to COVID-19 itself or whether there was an activation of PAP triggered by the infection. The course of PAP is variable, and the prognosis is unpredictable. Additionally, COVID-19 may determine exacerbation of symptoms and CT worsening in patients with PAP, and WLL may be an option in this scenario, especially in centers with low availability of GM-CSF therapy.

AUTHOR CONTRIBUTIONS

PFBC: study design; data collection; drafting and revision of the manuscript; and approval of the final version of the manuscript. NFS: data collection; drafting of the manuscript; and approval of the final version of the manuscript. RAK: study design; revision of the manuscript; and approval of the final version of the manuscript. BGB: study design; drafting and revision of the manuscript; and approval of the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers. 2019;5(1):16. https://doi.org/10.1038/s41572-019-0066-3
2. McCarthy C, Carey BC, Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2022;205(9):1016-1035. https://doi.org/10.1164/rccm.202112-2742SO
3. Beltramo G, Cottenet J, Mariet AS, Georges M, Piroth L, Tubert-Bitter P, et al. Chronic respiratory diseases are predictors of severe outcome in COVID-19 hospitalised patients: a nationwide study. Eur Respir J. 2021;58(6):2004474. https://doi.org/10.1183/13993003.04474-2020

4. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, et al. Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease. An International Multicenter Study. Am J Respir Crit Care Med. 2020;202(12):1656-1665. https://doi.org/10.1164/rccm.202007-2794OC
5. Baldi BG, Radzikowska E, Cottin V, Dilling DF, Ataya A, Carvalho CRR, et al. COVID-19 in Lymphangioleiomyomatosis: An International Study of Outcomes and Impact of Mechanistic Target of Rapamycin Inhibition. Chest. 2022;161(6):1589-1593. https://doi.org/10.1016/j.chest.2021.12.640
6. Papiris SA, Campo I, Mariani F, Kallieri M, Kolilekas L, Pappaioannou AI, et al. COVID-19 in patients with Pulmonary Alveolar Proteinosis: A European multicenter study. ERJ Open Res. 2022;00199-2022. Published 2022 Jul 14. https://doi.org/10.1183/23120541.00199-2022
7. Bonaventura A, Vecchié A, Wang TS, Lee E, Cremer PC, Carey B, et al. Targeting GM-CSF in COVID-19 Pneumonia: Rationale and Strategies. Front Immunol. 2020;11:1625. https://doi.org/10.3389/fimmu.2020.01625
8. Tazawa R, Ueda T, Abe M, Tatsumi K, Eda R, Kondoh S, et al. Inhaled GM-CSF for Pulmonary Alveolar Proteinosis. N Engl J Med. 2019;381(10):923-932. https://doi.org/10.1056/NEJMoa1816216