

Case Report



Pulmonary alveolar proteinosis or coronavirus disease 19 pneumonia: A clinical case study

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Abstract

The COVID-19 pandemic has resulted in a significant number of hospitalizations worldwide, complicating the diagnosis of rare respiratory diseases, such as pulmonary alveolar proteinosis (PAP), which can present with clinical symptoms and radiological findings similar to those of COVID-19. Consequently, accurate diagnosis is crucial. This report describes a case involving a young man with a history of progressive shortness of breath who was initially treated for COVID-19 pneumonia based on high-resolution computed tomography (HRCT) findings. However, following three negative polymerase chain reaction tests from the patient's throat swab and a lack of clinical improvement despite COVID-19 treatment, he underwent bronchoscopy and bronchoalveolar lavage. The results of these procedures demonstrated PAP. Given that COVID-19 presents with a wide range of manifestations and that HRCT of the lungs is currently the most sensitive diagnostic test for the disease, it is essential to consider the patient's medical history when diagnosing various pulmonary conditions. More precisely, a thorough assessment of the patient's history can significantly influence the diagnostic outcome.

Keywords: Pulmonary alveolar proteinosis, COVID-19, Differential diagnosis, PAP, Case report

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung syndrome characterized by the dysfunction of alveolar macrophages and the accumulation of surfactant lipids and proteins within the alveoli. This accumulation results in progressive hypoxic respiratory failure (1). A large-scale study reported the prevalence of PAP was approximately 6.8 cases per million in the United States (2). Activity-related dyspnea was the most commonly reported symptom, observed in 94% of PAP patients in the study conducted by Bonella et al (3). Additionally, some symptoms, such as coughing, fatigue, weight loss, and fever, have been documented among patients; however, some individuals may remain asymptomatic (4). PAP may result from minor sequence alterations in surfactant protein genes or genes encoding the granulocyte-macrophage colony-stimulating factor receptor. Other potential etiologies include toxin inhalation, anti-macrophage activating antibodies, and hematologic disorders (5). It is important to note that the "crazy paving" pattern is not exclusive to PAP; it can also be observed in various other pulmonary conditions, including infections, malignancies, pulmonary edema,

alveolar hemorrhage, organizing pneumonia, acute respiratory distress syndrome, *Pneumocystis pneumonia*, and lipid pneumonia. The diagnosis of PAP may be overlooked in the context of the COVID-19 infection, as their clinical presentations and radiological characteristics can be quite similar. Furthermore, there is currently no evidence to support the efficacy of corticosteroids in the treatment of autoimmune PAP (6). The progression of PAP can vary significantly, ranging from spontaneous recovery to fatal outcomes. The implementation of bronchoalveolar lavage has markedly improved the 5-year survival rate in cases of autoimmune PAP, reaching nearly 95%. However, patients diagnosed with PAP are at an increased risk of opportunistic infections, particularly from organisms such as *Aspergillus* spp., *Candida* spp., *Mycobacterium* (both tuberculous and non-tuberculous), *Nocardia*, and *Pneumocystis* spp. Further, approximately 30% of individuals with autoimmune PAP may develop pulmonary fibrosis (7).

The symptoms and imaging findings associated with PAP can closely resemble those observed in COVID-19 patients, making it challenging to differentiate between

the two conditions. PAP can be diagnosed based on characteristic findings from chest computed tomography (CT) scans, as well as through pathological or cytological specimens (5). It is important to note that lung CT scans are utilized in conjunction with other diagnostic procedures for COVID-19, a disease that accounted for a significant number of patients with respiratory issues admitted to hospitals during the pandemic.

During the COVID-19 pandemic, diagnosing rare lung diseases with symptoms similar to those of COVID-19 has posed a significant challenge. This case study presents a patient with PAP who was initially misdiagnosed with COVID-19 and improperly treated due to the overlapping clinical manifestations and imaging findings of the two diseases, coupled with the high prevalence of COVID-19. However, re-evaluation was conducted since the patient did not experience significant relief of symptoms following the standard treatment approach for COVID-19. This process involved a more thorough examination and a comprehensive review of the patient's history, leading to the correct diagnosis of PAP. The patient was subsequently treated appropriately. It is important to note that while diseases such as PAP can be self-limiting in some cases, most cases require prompt intervention to prevent complications (8).

Case Presentation

A 28-year-old male smoker was evaluated in the Emergency Department of Khorshid hospital in Isfahan, Iran, due to progressive dyspnea. He had been hospitalized at another facility for seven days before being referred to our hospital, as his symptoms had not improved. At that facility, the patient's reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 had returned negative; however, high-resolution computed tomography (HRCT) of the chest revealed diffuse bilateral smooth thickening of interlobular and intralobular septal lines, as well as ground-glass opacities consistent with a crazy-paving pattern, which is often associated with COVID-19 (Figure 1).

The patient was subsequently diagnosed with COVID-19 pneumonia. Notably, he had no history of fever, chills,



Figure 1. High-resolution computed tomography of the patient's lungs

hemoptysis, or productive cough. The treatment regimen included high-dose corticosteroids, specifically 100 mg of intravenous methylprednisolone administered daily for three consecutive days.

A thorough history revealed that the patient had experienced exertional dyspnea for the past four months, which had recently intensified. He reported no history of exposure to inhaled substances. Upon measuring vital signs in the emergency department, the patient was found to be afebrile, with normal blood pressure. However, his heart rate was elevated at 104 beats per minute, and his respiratory rate was 34 breaths per minute. Notably, his oxygen saturation (SpO_2) measured on room air was 70%, and when using an oxygen mask with a reservoir bag at a flow rate of 15 L per minute, his SpO_2 increased to 80%.

The patient presented with respiratory distress and hypoxic respiratory failure but remained alert throughout the evaluation. He was subsequently transferred to the intensive care unit, where laboratory tests revealed elevated inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate, and ferritin. Serum lactate dehydrogenase levels were measured at 860 U/L, while cardiac evaluation yielded unremarkable results. Notably, two RT-PCR tests for SARS-CoV-2 were negative. Given the patient's clinical history and lack of response to COVID-19 treatment, a fiberoptic bronchoscopy was performed after five days. The procedure was conducted under local anesthesia to maintain oxygenation, with the bronchoscope being introduced through a small opening in the reservoir mask. The bronchoalveolar lavage fluid (BALF) exhibited a milky appearance, and positive periodic acid-Schiff staining suggested the presence of PAP. Additionally, the BALF culture demonstrated the growth of the Gram-negative bacillus *Acinetobacter baumannii*. The patient was treated with meropenem based on the results of the bronchial lavage culture. To confirm the diagnosis, a transbronchial lung biopsy was performed, and a microscopic examination of the sample confirmed the diagnosis of PAP (Figure 2).

Due to the patient's severe symptoms and hypoxemia, whole lung lavage was performed under general anesthesia using a double-lumen endotracheal tube. The procedure was conducted in separate sessions for each lung in the operating room. Following the second lavage, the patient exhibited significant improvements in symptoms and was discharged after four days. He required supplemental oxygen to maintain an SpO_2 above 90% for approximately three weeks. Subsequently, his need for supplemental oxygen decreased and was ultimately discontinued for four weeks. The patient is currently living normally without the requirement for supplemental oxygen.

Discussion

PAP is a rare disease characterized by pulmonary alveolar involvement and a diverse range of symptoms, which may vary from asymptomatic presentations to respiratory

failure. Additionally, PAP can present with nonspecific symptoms, including dyspnea, dry cough, fatigue, fever, and weight loss. Notably, these symptoms are also commonly observed in respiratory infections, such as COVID-19 (3,4). Nonspecific laboratory and paraclinical findings further complicate the diagnosis of PAP. In the reported case, a patient presenting with shortness of breath was misdiagnosed with severe COVID-19 and subsequently treated with immunosuppressants. Given that patients with PAP are susceptible to lung infections due to impaired alveolar macrophage function, this individual developed a secondary bacterial respiratory infection. Following a comprehensive medical history and additional diagnostic procedures during hospitalization, PAP was correctly diagnosed, and the patient fully recovered with appropriate therapy. A significant factor contributing to the initial misdiagnosis was the timing of the disease presentation, which occurred in April 2020 at the onset of the COVID-19 pandemic. Moreover, the patient had close contact with several individuals diagnosed with COVID-19. During this period, PCR tests were regarded as the most reliable diagnostic tool for COVID-19, boasting a sensitivity of 97.3% (9). The occurrence of three negative PCR tests in this patient, yet the continued consideration of a COVID-19 diagnosis, highlights the heightened concern among physicians during the pandemic regarding the potential spread of the virus from undiagnosed cases. Consequently, clinicians prioritized the treatment of

patients presenting with fever as potential COVID-19 infections, often conducting multiple tests for the virus while inadvertently neglecting the screening for other underlying conditions (10). Other case reports have documented instances of misdiagnosing patients with COVID-19 during the pandemic (10,11). Furthermore, the prevalence of PAP is quite low, and numerous case reports have been published regarding this rare disease. Additionally, several cases of PAP following COVID-19 infection have been reported (6,12). Notably, to the best of our knowledge, only the report by Mastafa et al is in line with our case, where the misdiagnosis of PAP as COVID-19 pneumonia resulted in a delay in the treatment of a critically ill patient (13). A case study conducted in Spain reported a patient who presented with exacerbated dyspnea and an increase in cardiopulmonary function class from type II to III. This patient had no prior history of PAP, and a diagnosis of COVID-19 pneumonia was ruled out. Based on the findings from lung biopsy pathology, along with clinical, laboratory, and imaging evidence, a diagnosis of PAP was established, and the patient subsequently received appropriate treatment (11). The patient exhibited mild hypoxia and low levels of inflammatory markers, which warranted a lung biopsy due to his stable physical condition. In contrast, patients with moderate lung involvement from COVID-19 typically present with elevated inflammatory markers. [Table 1](#) summarizes the distinct and overlapping symptoms, as well as the diagnostic tools for PAP and

Table 1. Comparative Analysis of Symptoms and Diagnostic Tools in PAP and COVID-19

Similarities	Differences		
Common symptoms and diagnostic tools in PAP and COVID-19	Distinctive symptoms and diagnostic tools in PAP and COVID-19		
A broad spectrum of symptoms, ranging from asymptomatic presentation to respiratory failure	PAP	COVID-19	
Dyspnea, dry coughing, fatigue, fever, weight loss, and hypoxia	Finger clubbing	Crackles heard in lungs	PCR test results
Measurement of lactate dehydrogenase levels noted to increase in 80% of patients with PAP	Presence of clinical and distinctive symptoms	Detection of clonal anti-stimulus antibodies in the serum and alveolar lavage fluid in nearly all patients with autoimmune PAP	***
Lung CT scan	***	Bronchoscopy	***

Note. COVID-19: Coronavirus disease 19; PAP: Pulmonary alveolar proteinosis; PCR: Polymerase chain reaction; CT scan: Computed tomography scan.

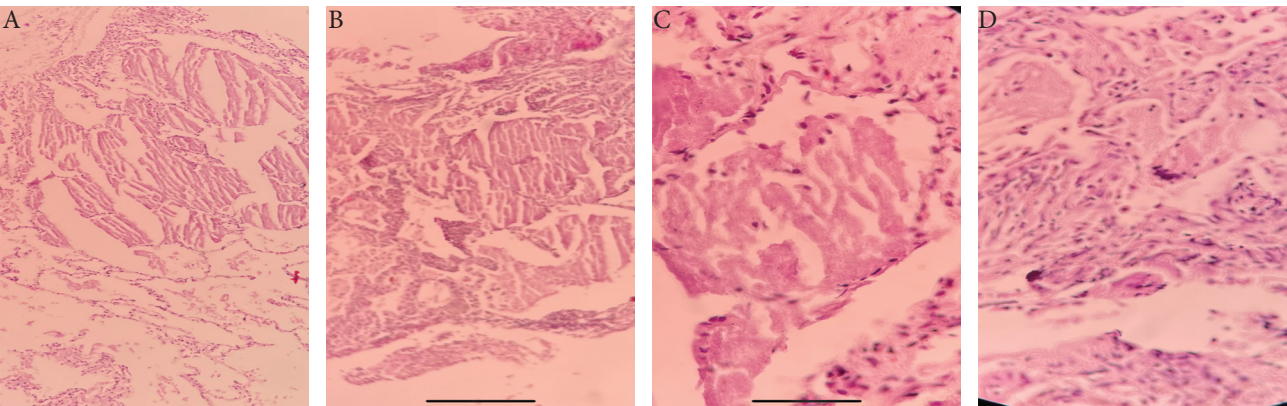


Figure 2. Histological examination revealing lung tissue with the accumulation of granular eosinophilic material and cholesterol clefts in alveolar spaces: low power and high power (**A, B, & C**) and multinucleated giant cells (**D**). Note. The alveolar spaces are filled with dense hyaline material, and multinucleated giant cells are also observed

COVID-19, based on a review of the literature (12,13).

Furthermore, symptoms in COVID-19 patients are typically acute, whereas they tend to be chronic in patients with PAP. In this study, diagnostic challenges arose due to the patients' severe pulmonary involvement, hypoxemia, and progression of the disease.

The presence of elevated inflammatory markers, an unclear history of PAP, and imaging findings resembling those of COVID-19 during the pandemic contributed to initial diagnostic errors, leading to the majority of hospitalized patients with respiratory symptoms being misdiagnosed with COVID-19. However, as the patient's clinical condition deteriorated, a more thorough re-evaluation was conducted, including a comprehensive history of the disease course. The patient subsequently underwent BAL. The appearance and pathological analysis of the obtained fluid facilitated the differential diagnosis between PAP and lung infection. A lung biopsy was performed, which confirmed the diagnosis of PAP. Ultimately, the patient's dramatic response to the therapeutic intervention of whole lung lavage definitively substantiated the diagnosis. The absence of systematic guidelines for the diagnosis and treatment of PAP further complicates the recognition of this condition. Additionally, clinicians must consider alternative diagnoses when a patient fails to respond to standard treatment.

Conclusion

Attending to rare causes of shortness of breath, such as PAP, is particularly important during the ongoing COVID-19 pandemic, as COVID-19 also presents with respiratory symptoms. This awareness can significantly enhance the likelihood of survival for affected patients. Given the distinct treatment approaches for PAP and COVID-19, as well as the increased risk of adverse effects associated with immunosuppressive therapies in PAP patients, accurate differentiation between these conditions is essential. COVID-19 often mimics other respiratory illnesses in both clinical and radiological presentations. Therefore, obtaining a comprehensive medical history and conducting a thorough examination of the disease course, symptoms, and laboratory findings can greatly assist physicians in distinguishing between the various causes of shortness of breath.

Authors' Contribution

Conceptualization: Huriyeh Hashemi, Amir Mohamad Mozafari.

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Competing Interests

The authors declare that they have no conflict of interests to disclose.

Ethical Approval

This article was approved by Isfahan University of Medical Sciences, with the ethical code IR.MUI.MED.REC.1400.713 (dated August 14, 2021, at 14:50:40).

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References

- Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. *N Engl J Med.* 1958;258(23):1123-42. doi: [10.1056/nejm195806052582301](https://doi.org/10.1056/nejm195806052582301).
- McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC. Prevalence and healthcare burden of pulmonary alveolar proteinosis. *Orphanet J Rare Dis.* 2018;13(1):129. doi: [10.1186/s13023-018-0846-y](https://doi.org/10.1186/s13023-018-0846-y).
- Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. *Respir Med.* 2011;105(12):1908-16. doi: [10.1016/j.rmed.2011.08.018](https://doi.org/10.1016/j.rmed.2011.08.018).
- Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med.* 2008;177(7):752-62. doi: [10.1164/rccm.200708-1271OC](https://doi.org/10.1164/rccm.200708-1271OC).
- Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, et al. Pulmonary alveolar proteinosis. *Eur Respir Rev.* 2011;20(120):98-107. doi: [10.1183/09059180.00001311](https://doi.org/10.1183/09059180.00001311).
- Salvaterra E, Campo I. Pulmonary alveolar proteinosis: from classification to therapy. *Breathe (Sheff).* 2020;16(2):200018. doi: [10.1183/20734735.0018-2020](https://doi.org/10.1183/20734735.0018-2020).
- Chiş AF, Man MA, Chiş BA, Pop CM. Alveolar proteinosis - an underdiagnosed condition in young people. *Med Pharm Rep.* 2021;94(Suppl No 1):S40-2. doi: [10.15386/MPR-2227](https://doi.org/10.15386/MPR-2227).
- Seymour JF, Begley CG, Dirksen U, Presneill JJ, Nicola NA, Moore PE, et al. Attenuated hematopoietic response to granulocyte-macrophage colony-stimulating factor in patients with acquired pulmonary alveolar proteinosis. *Blood.* 1998;92(8):2657-67.
- Binny RN, Priest P, French NP, Parry M, Lustig A, Hendy SC, et al. Sensitivity of reverse transcription polymerase chain reaction tests for severe acute respiratory syndrome coronavirus 2 through time. *J Infect Dis.* 2022;227(1):9-17. doi: [10.1093/infdis/jiac317](https://doi.org/10.1093/infdis/jiac317).
- Qin S, Lv D, Duan R, Zheng X, Bukai A, Lu X, et al. Case report: a case of brucellosis misdiagnosed as coronavirus disease 2019/influenza in China. *Front Public Health.* 2023;11:1186800. doi: [10.3389/fpubh.2023.1186800](https://doi.org/10.3389/fpubh.2023.1186800).
- Zoroufian A, Mohseni-Badalabadi R, Mahalleh M, Ghorashi SM, Momtahn S, Omid N. A potential misdiagnosis in the COVID-19 pandemic era: a case report of superimposed thrombosis or tumor recurrence. *J Cardiothorac Surg.* 2021;16(1):316. doi: [10.1186/s13019-021-01697-3](https://doi.org/10.1186/s13019-021-01697-3).
- Le-Khac B, Tran-Le QK, Nguyen-Ho L, Duong-Quy S. Post-COVID-19 pulmonary alveolar proteinosis treated successfully with whole lung lavage: a rare case report. *Pulm Ther.* 2023;9(2):287-93. doi: [10.1007/s41030-023-00224-0](https://doi.org/10.1007/s41030-023-00224-0).
- Sisman M, Karapolat S, Topaloglu O, Akdogan A, Turkyilmaz A. A case of pulmonary alveolar proteinosis misdiagnosed as COVID-19 pneumonia. *Cir Cir.* 2022;90(3):402-5. doi: [10.24875/ciru.21000746](https://doi.org/10.24875/ciru.21000746).