

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 June 16; 9(17): 4116-4459



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**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Pietro Scicchitano, MD, Professor, Research Scientist, Department of Emergency and Organ Transplantation, School of Medicine, University of Bari, Bari 70124, Italy. [piero.sc@hotmail.it](mailto:piero.sc@hotmail.it)

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Jia-Hui Li*; Production Department Director: *Yu-Jie Ma*; Editorial Office Director: *Jin-Lai Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

June 16, 2021

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<https://www.wjnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Pulmonary alveolar proteinosis complicated with tuberculosis: A case report

Hao Bai, Zi-Rui Meng, Bin-Wu Ying, Xue-Rong Chen

**ORCID number:** Hao Bai 0000-0002-0916-5755; Zi-Rui Meng 0000-0002-0509-200X; Bin-Wu Ying 0000-0001-8077-3908; Xue-Rong Chen 0000-0003-1156-0997.

**Author contributions:** Bai H and Meng ZR collected and analyzed the patient data, and were major contributors in writing the manuscript; Chen XR and Ying BW interpreted the patient data; all authors read and approved the final manuscript.

**Supported by** the National Science and Technology Major Project of the Ministry of Science and Technology of China, No. 2018ZX10715-003.

**Informed consent statement:** Case report analysis used anonymous data and unidentifiable images that were obtained after the patient agreed to treatment with written consent.

**Conflict-of-interest statement:** The authors have no conflicts of interest to disclose.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an

**Hao Bai, Zi-Rui Meng, Bin-Wu Ying,** Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

**Xue-Rong Chen,** Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

**Corresponding author:** Xue-Rong Chen, PhD, Chief Doctor, Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, No. 37 Guoxue Lane, Chengdu 610041, Sichuan Province, China. [xuerongchenchen@163.com](mailto:xuerongchenchen@163.com)

### Abstract

#### BACKGROUND

Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by the accumulation of phospholipoproteinaceous material in the alveoli. Cases of PAP complicated with tuberculosis are much more complex and have rarely been well recorded.

#### CASE SUMMARY

We describe a 21-year-old Han Chinese patient with suspicious lung infection associated with mild restrictive ventilatory dysfunction and diffusion reduction. High resolution computed tomography revealed a “crazy-paving” appearance and multiple pulmonary miliary nodules around the bronchi. Bronchoalveolar lavage demonstrated a small amount of periodic acid-Schiff positive proteinaceous materials. A serological test for the presence of a *Mycobacterium tuberculosis* antibody and an interferon-gamma release assay were both positive. The patient received a standard course of first-line anti-tuberculosis treatment after diagnostic bronchoalveolar lavage. To date, clinical remission has been achieved and maintained for five years.

#### CONCLUSION

In summary, the diagnosis of PAP complicated with tuberculosis was supported by a combination of clinical manifestations, imaging, pulmonary function, laboratory examinations, bronchoalveolar lavage, etc. This case highlighted that diagnostic bronchoalveolar lavage in combination with anti-tuberculosis treatment is a safe and effective option for mild PAP patients with tuberculosis.

**Key Words:** Pulmonary alveolar proteinosis; Pulmonary tuberculosis; Bronchoalveolar lavage; Case report

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**Manuscript source:** Unsolicited manuscript

**Specialty type:** Respiratory system

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): D  
Grade E (Poor): 0

**Received:** February 1, 2021

**Peer-review started:** February 1, 2021

**First decision:** February 25, 2021

**Revised:** March 12, 2021

**Accepted:** April 8, 2021

**Article in press:** April 8, 2021

**Published online:** June 16, 2021

**P-Reviewer:** Singhan N, Strainiene S

**S-Editor:** Gong ZM

**L-Editor:** Wang TQ

**P-Editor:** Li X



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**Core Tip:** Pulmonary alveolar proteinosis (PAP) complicated with tuberculosis is a rare clinical situation. This case highlighted that diagnostic bronchoalveolar lavage in combination with anti-tuberculosis treatment is a safe and effective option for mild PAP patients with tuberculosis. Bronchoalveolar lavage did not induce the dissemination of tuberculosis because anti-tuberculosis drugs were used immediately.

**Citation:** Bai H, Meng ZR, Ying BW, Chen XR. Pulmonary alveolar proteinosis complicated with tuberculosis: A case report. *World J Clin Cases* 2021; 9(17): 4400-4407

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i17/4400.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i17.4400>

## INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is an unusual diffuse lung disease characterized by the accumulation of large amounts of periodic acid-Schiff (PAS) positive phospholipoproteinaceous material in the alveoli, and the prevalence of PAP is approximately seven cases per million population[1]. The major symptoms of PAP are progressive dyspnea, cough, fatigue, weight loss, and low-grade fever, all of which may also occur in tuberculosis. However, when PAP is complicated with tuberculosis, it is much more complex and has rarely been well recorded. Here, we present a successfully diagnosed and treated case of PAP with tuberculosis and review the main characteristics of other previously reported cases of PAP complicated with tuberculosis to obtain a better understanding of this situation.

## CASE PRESENTATION

### Chief complaints

Nonproductive cough for 2 mo.

### History of present illness

The patient was a 21-year-old Han Chinese man. He had no history of smoking, but he suffered from a nonproductive cough for 2 mo, accompanied by a low-grade fever (ranging from 37.4-37.8 °C) and night sweats; however, he denied hemoptysis, chills, weight loss, dyspnea, and other symptoms. Then he developed paroxysmal chest stabbing pain for 1 wk.

### History of past illness

The patient had no known history of a past illness.

### Personal and family history

The patient had no known personal and family history.

### Physical examination

Physical examination showed normal auscultation of both lungs, oxygen saturation of 98%, blood pressure of 126/75 mmHg, a temperature of 36.5 °C, respiratory rate of 20 times per minute, and pulse of 88 beats per minute. He had no clubbing, a pale complexion, or cyanosis.

### Laboratory examinations

Laboratory inspection revealed a white blood cell (WBC) count of  $10.01 \times 10^9/L$  with 79.10% neutrophils, and serological detection for *Mycobacterium tuberculosis* (*M. tuberculosis*) antibody was positive. The erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and Fungitec G test results were normal.

### Imaging examinations

Computerized tomography of the chest demonstrated increased lung texture and multiple patchy enhanced densities of both lungs, especially in the upper lobes, with no obvious adhesion to the pleurae. There were no abnormalities in the bronchi under the broncho fiberscope.

## FURTHER DIAGNOSTIC WORK-UP

The patient was admitted to West China Hospital. During hospitalization, comprehensive examinations were performed. Laboratory analyses revealed WBC  $5.74 \times 10^9$  /L, C-reactive protein 15.60 mg/L, interleukin-6 19.26 pg/mL, PCT 0.05 ng/mL, and ESR 32.0 mm/h, and his interferon-gamma release assay was positive. Arterial blood gases showed SpO<sub>2</sub> 93.4%, PaO<sub>2</sub> 64.8 mmHg, PaCO<sub>2</sub> 42 mmHg, and pH 7.40 (the detailed laboratory results are presented in Table 1). Meanwhile, the pulmonary function test revealed mild restrictive ventilation dysfunction and diffuse dysfunction. High-resolution computerized tomography (HRCT) revealed multiple pulmonary miliary nodules distributed around the bronchi, which were flake-like, patchy aggregates, mainly located in the upper lobes (Figure 1). Furthermore, fiberoptic bronchoscopy with transbronchial lung biopsy and diagnostic bronchoalveolar lavage was performed. Grey-white lung tissue was obtained from the apical segment of the right upper lung, and the pathological examination of the lung tissue showed mild inflammation. The acid-fast staining and Gomori's methenamine silver staining of the lung tissue were negative, but it was positive for Alcian blue (AB) staining (Figure 2). More importantly, the bronchoalveolar lavage fluid from the upper lungs appeared light and milky, and additional positive AB and PAS staining (eosinophilic granular) of proteins was found in the bronchoalveolar lavage fluid.

## FINAL DIAGNOSIS

The final diagnosis of the patient was PAP complicated with tuberculosis. The diagnosis of PAP was mainly based on eosinophilic PAS-positive proteins found in his bronchoalveolar lavage fluid. The diagnosis of tuberculosis was mainly based on positive results of *M. tuberculosis* antibody and interferon-gamma release assays and was finally confirmed by anti-tuberculosis treatment.

## TREATMENT

Initially, the patient was diagnosed with a pulmonary infection and was treated with azithromycin (0.5 g, intravenous, once a day) and doxycycline (0.2 g, oral, once a day), after which his cough was reduced, but the shadows of the lungs remained the same. Then, we revised the diagnosis to PAP complicated with tuberculosis. The patient received standard anti-tuberculosis treatment for 6 mo (isoniazid, rifampicin, pyrazinamide, and ethambutol treatment for 2 mo, followed by isoniazid and rifampicin treatment for 4 mo).

## OUTCOME AND FOLLOW-UP

As expected, all symptoms disappeared and the lesions of both lungs were significantly absorbed with a normal density demonstrated on HRCT (Figure 1) after 6 mo of anti-tuberculosis treatment. The patient has been followed up for 5 years, during which a clinical remission has been achieved and maintained. And the patient needs to visit the doctor if any symptom occurs again.

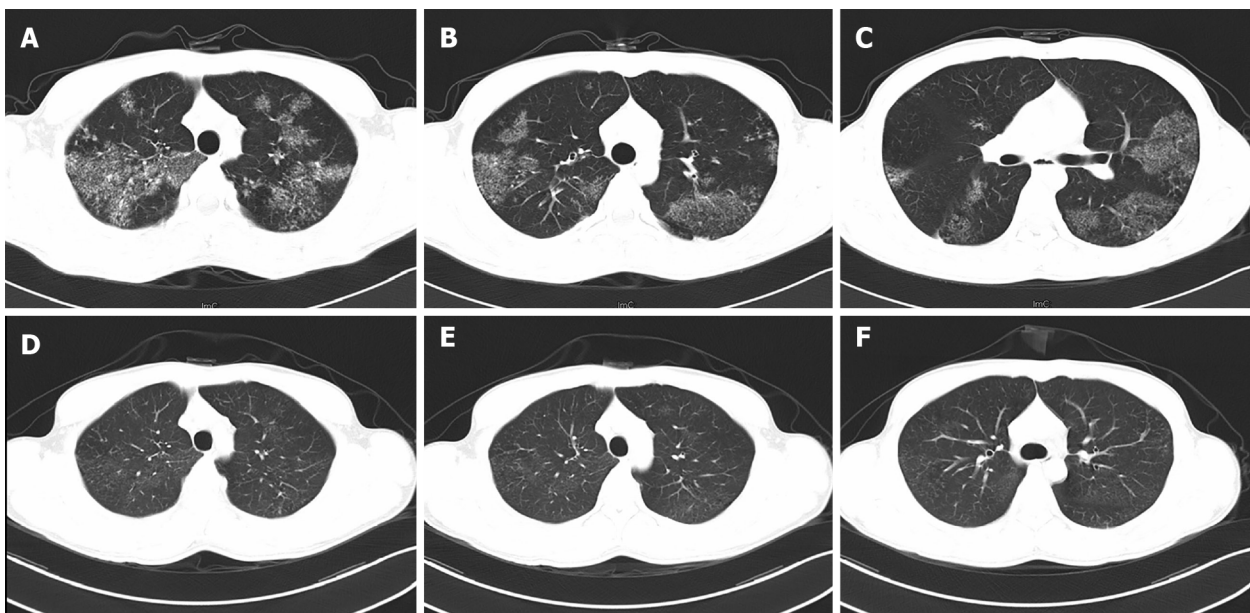
## DISCUSSION

According to the pathogenesis and clinical features, PAP is divided into three categories: congenital, secondary, and idiopathic. Congenital PAP mainly occurs in infants and is caused by mutations in surfactant proteins (SP) and granulocyte-

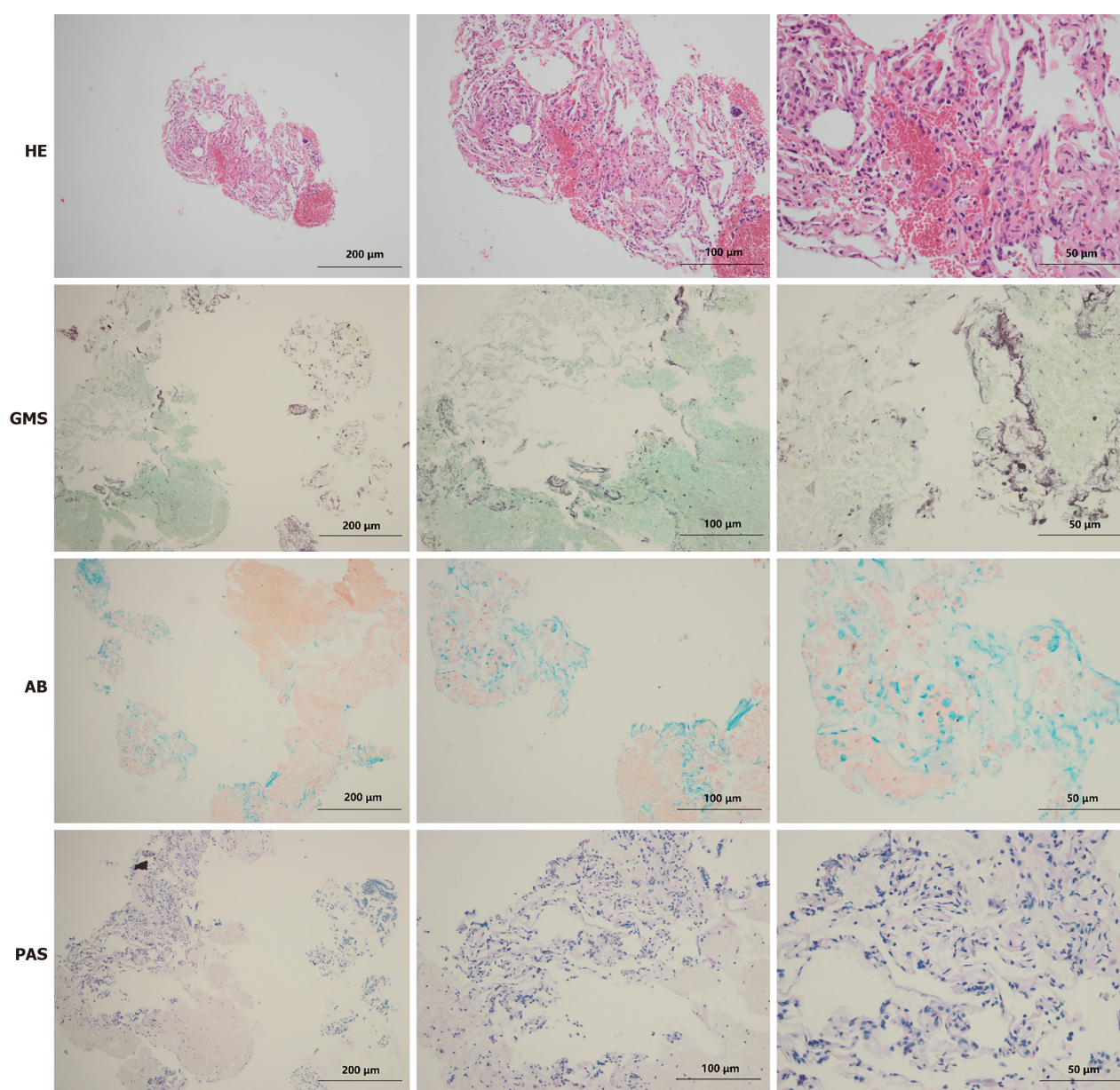


**Table 1** Laboratory results of the patient performed at West China Hospital

Laboratory examination	Result	Reference range
White blood cells ( $\times 10^9/L$ )	5.74	3.5-9.5
Red blood cells ( $\times 10^{12}/L$ )	5.28	4.3-5.8
Platelets ( $\times 10^9/L$ )	227	100-300
Prothrombin time (s)	13.7 ↑	9.6-12.8
International normalized ratio	1.17 ↑	0.88-1.15
Erythrocyte sedimentation rate (mm/h)	32.0 ↑	< 21
C-reactive protein (mg/L)	15.60 ↑	< 5
Interleukin-6 (pg/mL)	19.26 ↑	0.00-7.00
Procalcitonin (ng/mL)	0.05 ↑	< 0.046
Arterial blood gases		
SpO <sub>2</sub> (%)	93.4 ↓	95-98
PaO <sub>2</sub> (mmHg)	64.8 ↓	80-100
PaCO <sub>2</sub> (mmHg)	42	35-45
pH	7.40	7.35-7.45
Interferon-gamma release assay	Positive	Negative
<i>Mycobacterium tuberculosis</i> antibody	Positive	Negative

**Figure 1** High-resolution computerized tomography scans of the chest. A-C: Images before bronchoalveolar lavage and anti-tuberculosis treatment; D-F: Images after bronchoalveolar lavage and 6 mo of anti-tuberculosis treatment.

macrophage colony-stimulating factor (GM-CSF) receptor genes. Secondary PAP is associated with various underlying diseases, such as hematological malignancies, infections, and other diseases that cause severely low immune function or is associated with the inhalation of inorganic minerals or chemicals[2]. Approximately 90% of PAP cases are idiopathic, also known as autoimmune PAP, which is associated with the presence of anti-GM-CSF autoantibodies[3,4]. Of note, recent discoveries have suggested that there is an overlap between secondary PAP and idiopathic PAP, and impairments in the GM-CSF production pathway result in the majority of PAP cases [5,6].



**Figure 2 Histological examinations of lung biopsy.** HE: Hematoxylin-eosin staining; GMS: Gomori's methenamine silver staining; AB: Alcian blue staining; PAS: Periodic acid-Schiff staining.

With an insidious onset, the course of PAP lasts months to years. The clinical manifestations of PAP vary and are nonspecific, among which progressive dyspnea and nonproductive cough are the most common symptoms. Approximately one-third of patients are asymptomatic at presentation, while the majority present acutely with rapid progression to respiratory failure[7]. Physical examination often shows normal vital signs, although clubbing, cyanosis, and inspiratory crackles have been reported in individual cases. Typical lung dysfunction is restrictive ventilation dysfunction and diffuse dysfunction, and the imaging change is a “crazy-paving” pattern[8]. Although the “crazy-paving” pattern has been well-accepted to be associated with PAP, it is neither specific nor sensitive to diagnose PAP because several other diseases also have the same signs[9].

Notably, there are clear associations between PAP and tuberculosis. GM-CSF is critical for regulating alveolar macrophage function and maintaining homeostasis, by binding with macrophage surface receptors and then mediating signal transduction, macrophage terminal differentiation, intracellular lipid metabolism, surfactant catabolism, and pathogenic receptor expression[10]. Recent discoveries have suggested that individuals with deficient GM-CSF subsequently experience alveolar macrophage dysfunction and reduced elimination of both endogenous SP and exogenous *M. tuberculosis*; thus, these patients are susceptible to PAP and tuberculosis[11]. In PAP

**Table 2** Main characteristics of previously reported cases of pulmonary alveolar proteinosis complicated by tuberculosis

Ref.	Country	Sex	Age	Main manifestations	Sequential order	Diagnosis method	Main treatment	Prognosis	Other diseases
Ramirez[14], 1967	United States	Male	48	Pulmonary infiltrates	TB before PAP	Open lung biopsy	Bronchopulmonary lavage	Remission	None
Lathan <i>et al</i> [15], 1971	United States	Female	41	Chills, fever, productive cough, diffuse pulmonary infiltrates, and progressive dyspnea	PAP before TB	Open lung biopsy	Single lung lavage	Remission	None
Reyes and Putong[13], 1980	United States	Female	32	Fever, cough, and pulmonary cavities	TB before PAP	Open lung biopsy	Bronchopulmonary lavage	Unknown	Total gastrectomy and alcoholic hepatitis
Rekha <i>et al</i> [16], 1996	India	Male	26	Dyspnea and dry cough	PAP before TB	Open lung biopsy	Anti-tuberculosis therapy	Remission	None
Pereira-Silva <i>et al</i> [17], 2002	Brazil	Female	35	Dry cough, chest pain, mild dyspnea, and fever	At the same time	Open lung biopsy	Bronchoalveolar lavage	Unknown	Diabetes mellitus
Mayoralas Alises <i>et al</i> [18], 2003	Spain	Female	41	Night sweats, dyspnea, productive cough, and weight loss	TB before PAP	Bronchoscopy	Bronchoalveolar lavage	Remission	None
Yin <i>et al</i> [19], 2008	China	Female	17	Cough, expectoration, dyspnea on exertion, fever, and night sweats	At the same time	Transbronchial biopsy	Anti-tuberculous therapy and lung lavage	Improve	None
Tekgöl <i>et al</i> [20], 2012	Turkey	Male	46	Dyspnea, cough, and fever	PAP before TB	Transbronchial biopsy	Anti-tuberculosis therapy	Improve	None
Huang <i>et al</i> [21], 2012	China	Male	35	Dyspnea and productive cough	TB before PAP	Bronchoalveolar lavage	Whole lung lavage	Improve	Partial gastrectomy and aspergilloma
Cheraghvandi <i>et al</i> [22], 2014	Iran	Male	29	Progressive dyspnea, weakness, cough, fever, and chills	TB before PAP	Transbronchial biopsy	Anti-tuberculosis therapy	Died	Acute silicosis
Nimmatoori <i>et al</i> [23], 2020	United States	Male	32	Progressive dry cough and breathlessness	TB before PAP	Bronchoalveolar lavage	Whole lung lavage	Remission	None

PAP: Pulmonary alveolar proteinosis; TB: Tuberculosis.

cases, gene mutation or GM-CSF antibodies lead to macrophage dysfunction and an imbalance in surfactants. Increases in SP-A and SP-D, on the one hand, promote macrophages to engulf *M. tuberculosis* and, on the other hand, they compromise the function of macrophages[12]. In contrast, tuberculosis may also be the primary event, stimulating type II pneumocytes to secrete excess surfactant, thus triggering the development of PAP[13]. In the present case, PAP and tuberculosis were found at the same time, so it is difficult to tell whether tuberculosis was involved as a superinfection of PAP or whether the PAP was secondary to the tuberculosis.

Tuberculosis may increase the risk of developing PAP, and PAP patients may also develop secondary tuberculosis. There are common symptoms of PAP and tuberculosis, which will lead to a missed diagnosis or misdiagnosis. However, cases of PAP complicated with tuberculosis have rarely been well recorded (Table 2)[13-23]. Empirically, we need to be vigilant about the following signals in PAP patients, which indicate the presence of tuberculosis infection. First, the patient suffers from symptoms such as hemoptysis, fever, or night sweats, which are common in tuberculosis but infrequent in PAP. Second, chest radiography shows nodules, fibrous stripes, or consolidation, which are hard to explain in PAP. Third, the pulmonary function test reveals obstructive ventilation dysfunction. Last, the PPD skin test is strongly positive, or the pulmonary lesions are absorbed after anti-tuberculosis treatment.

The standard therapy for idiopathic PAP is therapeutic alveolar lavage, covering bronchoalveolar lavage and whole lung lavage. The basic theory underlying alveolar lavage is the reactivation of alveolar macrophages through mechanical clearance of



deposited lipids, proteins, and materials. In addition, systemic replacement therapy based on exogenous GM-CSF has been investigated and even used as an alternative to alveolar lavage[24]. Depleting B lymphocytes by rituximab and plasmapheresis are two new approaches to reduce the number of GM-CSF autoantibodies, which offers another promising way to cure those who are unsuccessfully treated by alveolar lavage and exogenous GM-CSF[25].

However, the treatment is more complicated when PAP is accompanied by tuberculosis. A combination of alveolar lavage and anti-tuberculosis chemotherapy has been proven to be the most effective way to treat tuberculosis-associated PAP, but the implementation of alveolar lavage can disseminate the tuberculosis. To date, most reports have suggested that alveolar lavage should be performed early after anti-tuberculosis drugs are used, but the best lavage treatment opportunity remains to be explored. In this study, the correct diagnosis was not made until after diagnostic bronchoalveolar lavage was performed, and then anti-tuberculosis drugs were used immediately. We presented a successfully treated PAP case complicated with tuberculosis, thus providing a feasible treatment option for such a situation.

## CONCLUSION

In summary, the diagnosis of PAP complicated with tuberculosis was supported by the combination of clinical manifestations, imaging, pulmonary function, laboratory examinations, bronchoalveolar lavage, *etc.* Diagnostic bronchoalveolar lavage in combination with anti-tuberculosis treatment is a safe and effective option for mild PAP patients with tuberculosis.

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