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**Pulmonary alveolar proteinosis complicated with tuberculosis: a case report**

Bai H *et al*. PAP complicated with tuberculosis

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**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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**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.

**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 ℃) 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 ℃, 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 × 109/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 abnormities 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 × 109/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 SpO2 93.4%, PaO2 64.8 mmHg, PaCO2 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-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].

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 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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**Footnotes**

**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.

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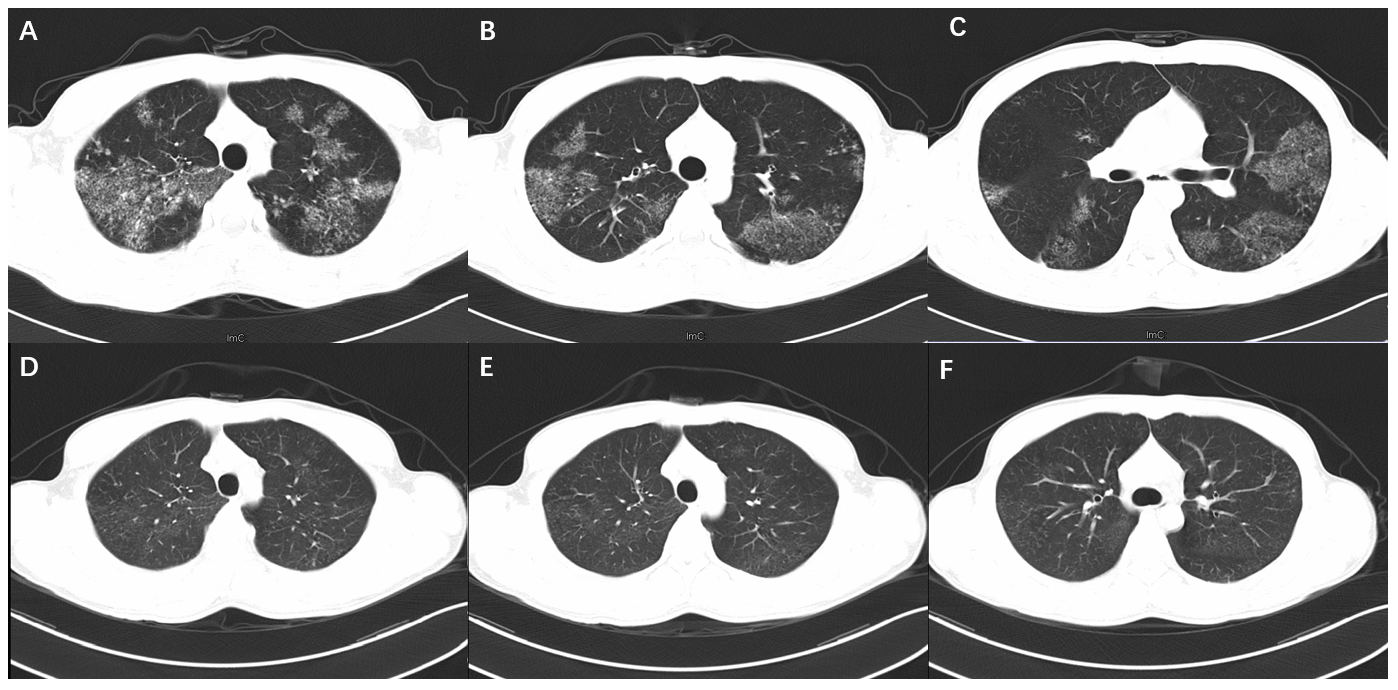
Grade C (Good): 0

Grade D (Fair): D

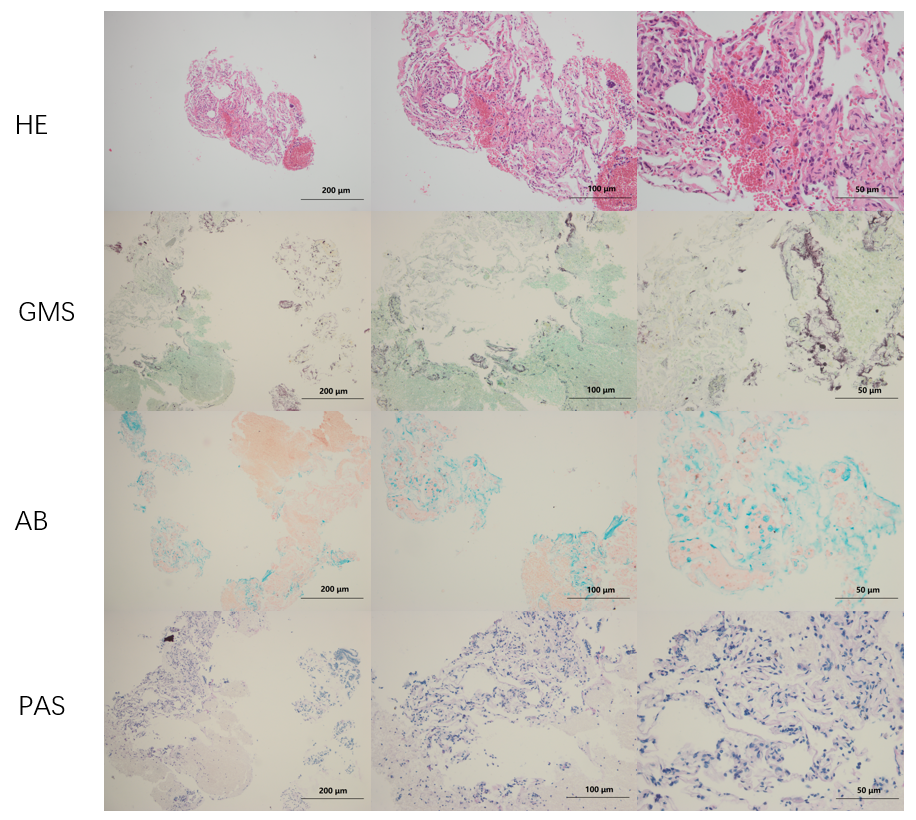
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**Figure Legends**



**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.



**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.

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

|  |  |  |
| --- | --- | --- |
| **Laboratory examination** | **Result** | **Reference range** |
| White blood cells (× 109/L) | 5.74 | 3.5-9.5 |
| Red blood cells (× 1012/L) | 5.28 | 4.3-5.8 |
| Platelets (× 109/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 |  |  |
| SpO2 (%) | 93.4 ↓ | 95-98 |
| PaO2 (mmHg) | 64.8 ↓ | 80-100 |
| PaCO2 (mmHg) | 42 | 35-45 |
| pH | 7.40 | 7.35-7.45 |
| Interferon-gamma release assay | positive | negative |
| *Mycobacterium tuberculosis* antibody | positive | negative |

**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 *et al*[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 *et al*[16], 1996 | India | male | 26 | dyspnea and dry cough | PAP before TB | open lung biopsy | anti-tuberculosis therapy | remission | none |
| Pereira-silva *et al*[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 *et al*[18], 2003 | Spain | female | 41 | night sweats, dyspnea, productive cough, and weight loss | TB before PAP | bronchoscopy | bronchoalveolar lavage | remission | none |
| Yin *et al*[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 |
| Tekgül *et al*[20], 2012 | Turkey | male | 46 | dyspnea, cough, and fever | PAP before TB | transbronchial biopsy | anti-tuberculosis therapy | improve | none |
| Huang *et al*[21], 2012 | China | male | 35 | dyspnea and productive cough | TB before PAP | bronchoalveolar lavage | whole lung lavage | improve | partial gastrectomy and aspergilloma |
| Cheraghvandi *et al*[22], 2014 | Iran | male | 29 | progressive dyspnea, weakness, cough, fever, and chills | TB before PAP | transbronchial biopsy | anti-tuberculosis therapy | died | acute silicosis |
| Nimmatoori *et al*[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.