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Complete remission of pulmonary alveolar proteinosis after anti-tuberculous chemotherapy: a case report

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare respiratory system disorder. Patients with PAP are at risk for a wide variety of secondary infections. This current case report describes a patient with PAP complicated by tuberculosis. A 48-year-old male patient with multiple follow-up chest computed tomography scans that showed predominant diffuse ground glass opacity in both lung fields, presented a few years later with new calcified lesions and pleural effusion. At this point, the associated auxiliary examination indicated the possibility of PAP combined with tuberculosis infection. The patient achieved complete remission after anti-tuberculosis treatment. PAP is an easily overlooked clinical syndrome due to its low prevalence and lack of specific clinical manifestations, especially when combined with other pulmonary lesions. Therefore, clinicians should consider this rare disease in patients presenting with pulmonary disease and plan for its co-morbidity with other secondary outcomes, such as opportunistic infections, which are a common and life-threatening complication in patients with PAP. This case indicates the possibility that anti-tuberculosis therapy can improve alveolar proteinosis in patients with PAP and secondary *Mycobacterium tuberculosis* infection.

Keywords

Pulmonary alveolar proteinosis, secondary infection, tuberculosis, rare disease, case report

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare respiratory system disorder, which is caused by the abnormal accumulation of intra-alveolar surfactant, causing hypoxic respiratory dysfunction and increased risk of concurrent infection.[1–3] The susceptibility to pulmonary infection is an important feature of this disease, sometimes with opportunistic organisms.[2] These opportunistic pathogens can be *Aspergillus*,[4] *Nocardia*,[5] *Histoplasma capsulatum*,[6] *Cryptococcus neoformans*,[7] *Pneumocystis carinii*,[8] *Cytomegalovirus*[9] and *Mycobacteria*.[10–13] Opportunistic infections are associated with a poor prognosis and high mortality rate. For example, a comprehensive review of the literature that identified all reported cases of PAP and opportunistic infections between 1950 and July 2010 found that the overall survival rate was only 56% (39 of 70 patients) and 31 of 70 patients (44%) died during the follow-up period.[14] Opportunistic infections occur in 5–13% of patients and account for 18–20% of deaths.[1,3,15] Of PAP patients with an opportunistic infection, those with a *Mycobacteria* infection had the highest survival rate (70%).[14] *Mycobacterium tuberculosis* infection occurs in 2–5% of patients with PAP[15–17] and accounts for 37% of all opportunistic infections.[14] The pathological mechanisms that underlie the predisposition to local and systemic infections in patients with PAP are not clear. Research has shown that the alveolar material from patients with PAP is a good medium for *M. tuberculosis*.[18] The presence of granulocyte–macrophage colony-stimulating factor (GM-CS) autoantibodies interferes with the terminal differentiation of macrophages,[19] leading to macrophage dysfunction and further increasing susceptibility.[14,20]

This current case report describes a middle-aged male smoker with PAP complicated with a *M. tuberculosis* infection that achieved complete remission after anti-tuberculous chemotherapy.

Case report

In May 2015, a 43-year-old male patient presented to the Department of Imaging, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, China with no obvious symptoms but he reported a 3-year history of lung lesions. He worked as a national civil servant and had a smoking history of more than 20 years. He had no history of surgery, trauma or a family history of pulmonary disease. A previous physical examination in July 2012 revealed multiple ground-glass and hazy opacities in both lungs. After that earlier examination, the patient did not receive a specific diagnosis or treatment. Intermittent chest computed tomography (CT) examinations showed that the pulmonary lesions were roughly the same as before (Figures 1a–1c).

In order to confirm a diagnosis, the 43-year-old male patient was admitted to the Department of Imaging, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, China in May 2015 with a history of the identification of lung lesions 3 years previously; and he did not have any of the following symptoms of coughing, fever, chest tightness or haemoptysis. Chest X-ray examination showed bilateral upper lung field lesions (Figure 2). He was hospitalized and video-assisted right thoracotomy surgery, lysis of pleural adhesion and right upper lobe wedge resection were performed. Postoperative pathological examination of a lesion from the right upper lobe showed scattered periodic acid–Schiff staining and was consistent with pulmonary alveolar proteinosis (Figure 3). After anti-inflammatory treatment (0.5 g azithromycin, oral, once a day for 5 days), CT imaging showed absorption of the lesions

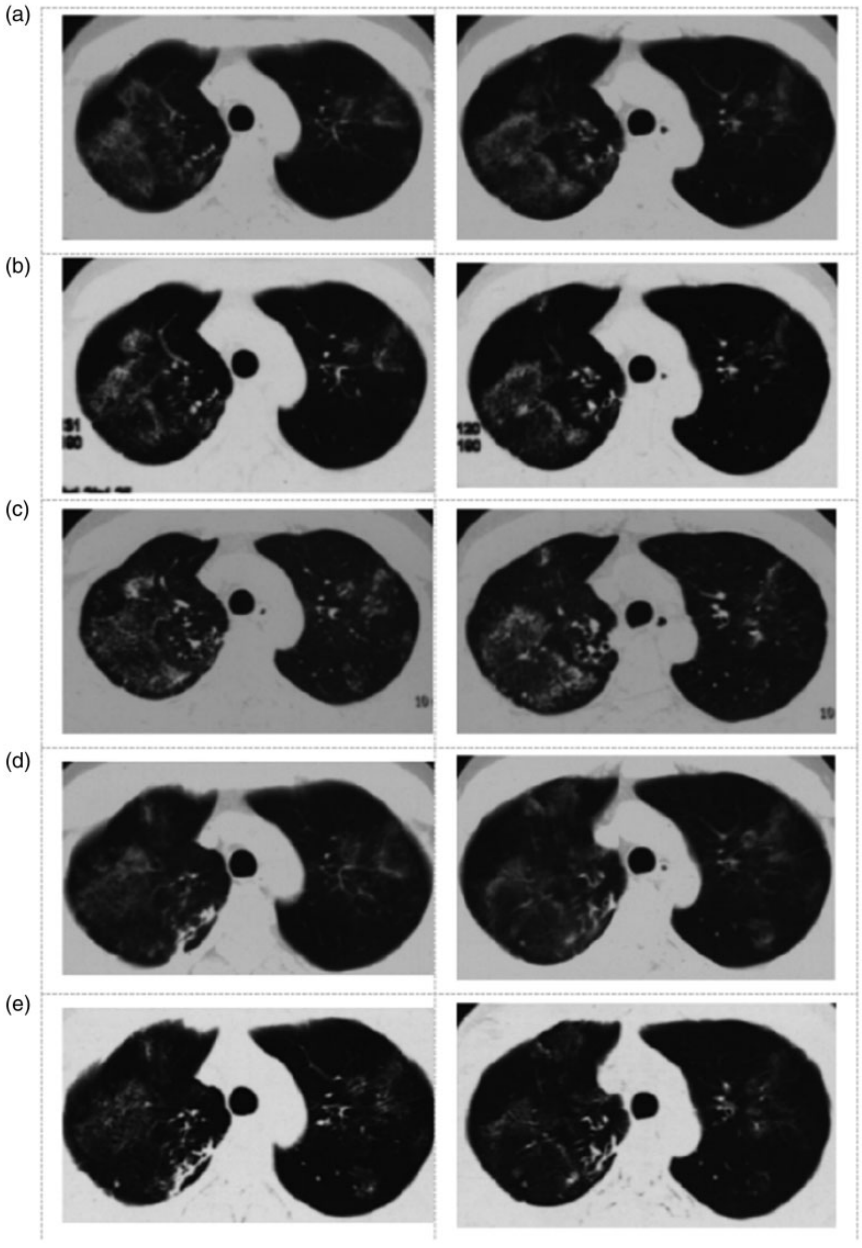

Figure 1. Chest computed tomography (CT) images of a male patient: (a–c) images taken before his first hospitalization showing three CT scans taken at incremental time-points over 9 months after the accidental discovery of lung lesions (a: 9 September 2014; b: 17 September 2014; c: 15 May 2015). The CT images show persistent multiple ground glass opacity in both lungs with little change between the three time-points, especially in the right lung and (d & e) images from 4 and 6 months after hospital discharge showing focused shrinkage and less dense lesions (d: September 2015; e: November 2015).

(Figures 1d & 1e). There was no discomfort reported by the patient after discharge from hospital.

At 7 months after the operation, after accidentally catching an upper respiratory tract infection, the patient developed a fever (highest temperature was 38.5°C), pharyngeal itching, a paroxysmal cough, a small amount of white foam sputum, shortness of breath, chest tightness, dyspnoea and chest pain. The patient underwent a chest CT examination, which showed alterations to the pulmonary interstitial tissue and right pleural effusion (Figure 4). A week later, in January 2016, he was admitted to the Department of Imaging, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, China. An ultrasound examination showed a large effusion in the right pleural cavity. Routine examination of the pleural effusion demonstrated the following findings: Rivalta Test positive; no malignant cells; tuberculosis antibody positive; and TB-SPOT positive. These findings suggested the possibility of tuberculous pleurisy. After pleural puncture, CT examination showed a small amount of effusion in the right pleural cavity, pulmonary infectious lesions and a high possibility of tuberculosis. From the first day after the CT examination, anti-tuberculosis treatment was provided. He received 6 months of standard anti-tuberculosis treatment (300 mg isoniazid oral, 450 mg rifampicin oral, 1500 mg

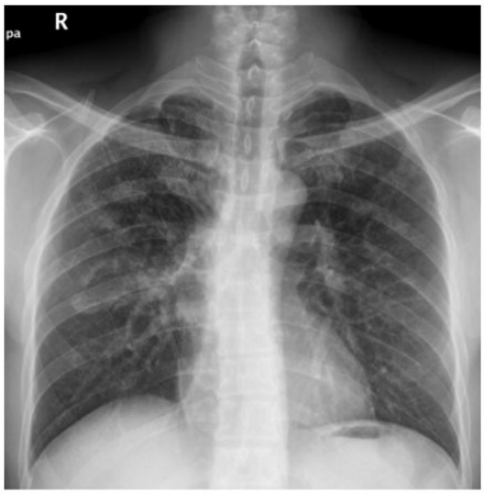

Figure 2. A chest X-ray undertaken before surgery in May 2015 that shows multiple patchy and nodular increased density in the middle and upper field of both lungs with visible strip shadows. The right hilar shadow was slightly thicker and the left hilar shadow was still clear. There was no heart enlargement.

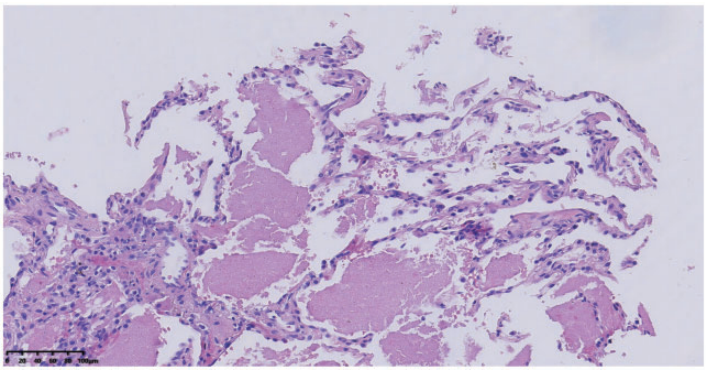

Figure 3. Representative photomicrograph of a pathological specimen of a lesion from the right upper lobe that showed that the alveoli were filled with eosinophilic material and there was preservation of the normal lung architecture. The lesion was consistent with pulmonary alveolar proteinosis. Haematoxylin and eosin; scale bar 20–100 μm. The colour version of this figure is available at: http://imr.sagepub.com.

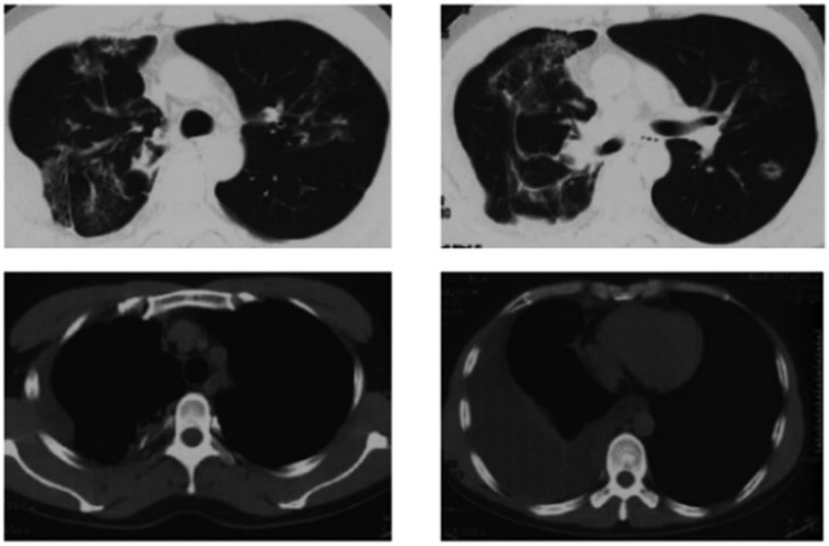

Figure 4. Chest computed tomography images undertaken in December 2015 after the patient accidentally contracted an upper respiratory tract infection at 7 months after surgery. The images show multiple interstitial lesions in both lungs, especially in the right lung, with localized emphysema and effusion in the right thoracic cavity.

pyrazinamide oral and 800 mg ethambutol oral, all three times a week for 2 months; and the follow-up phase included 450 mg rifampicin oral and 300 mg isoniazid oral, both three times a week, for a further 4 months). The anti-tuberculosis treatment lasted for 6 months through whole-course supervision, during which the liver and kidney function was checked regularly and no serious dysfunction occurred. The patient returned for six chest CT examinations from the start of the anti-tuberculosis treatment. The imaging findings showed gradual improvement and no signs of recurrence (Figure 5). During the whole follow-up period, the patient reported no discomfort. The reporting of this study conforms to CARE guidelines.[21] Written informed consent was obtained from the patient.

Discussion

Pulmonary alveolar proteinosis is a rare diffuse lung disorder with an accumulation of surfactant in the pulmonary alveoli and dysfunction of alveolar macrophages,[1,2,22] which is often overlooked in clinical practice, especially when combined with other pulmonary lesions. PAP is classified in accordance with the underlying pathogenetic mechanism as primary, secondary or congenital.[1] Autoantibodies against GM-CSF are related to autoimmune PAP,[23] which neutralize the bioactivity of GM-CSF[24] and impairs the clearance of surfactants leading to the disease.[25] Secondary PAP patients are negative for anti-GM-CSF antibodies, which can help to distinguish autoimmune PAP from secondary PAP.[20]

Although the therapeutic approach to PAP is closely related to the pathogenic form and severity of the disease, whole-lung lavage (WLL) is still the current gold standard of care for patients with PAP.[26] When PAP is associated with *M. tuberculosis* infection, treatment becomes more complicated. A previous study demonstrated that the alveolar

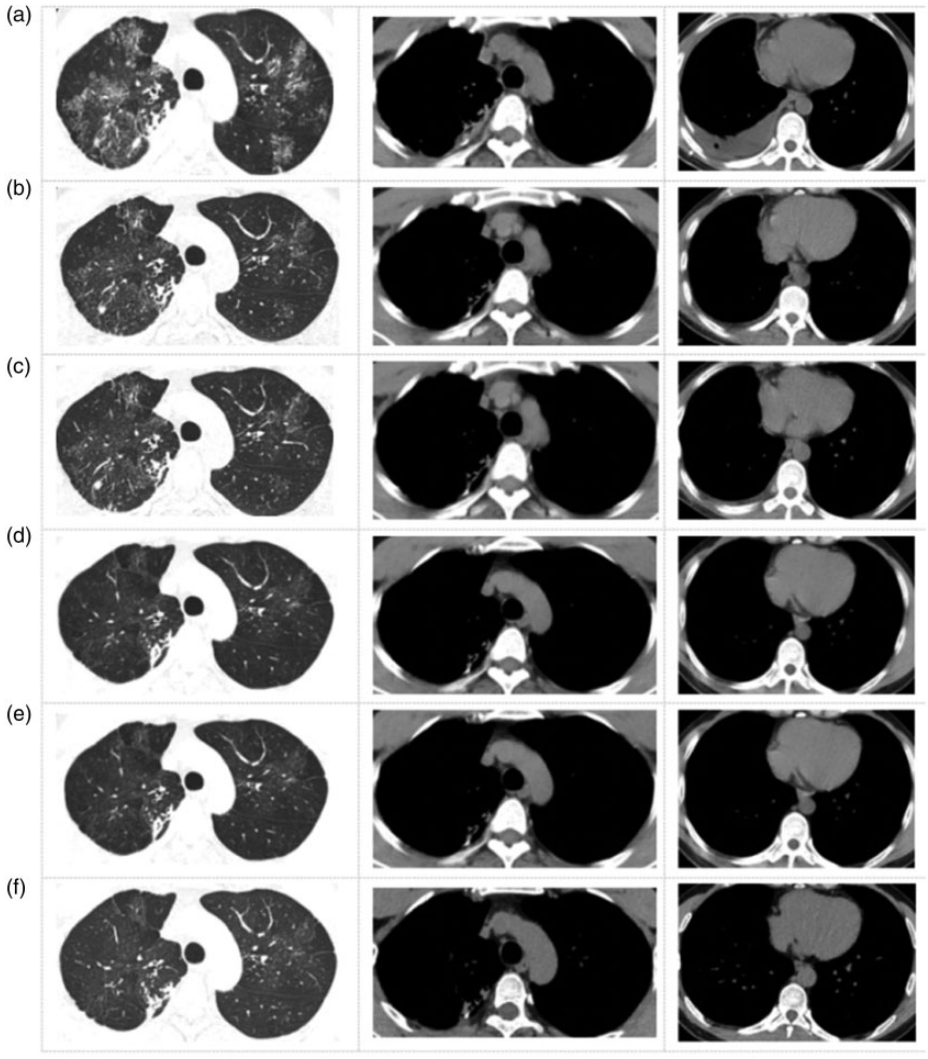

Figure 5. Chest computed tomography (CT) images: (a) images taken in January 2016 during the patient's second hospitalization at 1 week after contracting an upper respiratory tract infection. The images show the following: multiple patches and small nodular densities in both lungs; the edge was blurred; the right pleura was thickened; nodular calcification was seen; a small amount of effusion was seen in the right pleural cavity; punctate gas shadow was seen in the right pleural cavity; there were multiple small lymph nodes in the mediastinum, which indicated pulmonary infectious lesions and a high possibility of tuberculosis infection and (b–f) images showing that the lung lesions and thickened pleura gradually improved and the pleural effusion was completely absorbed (b: February 2016; c: May 2016; d: September 2016; e: May 2018; f: December 2019).

material in patients with alveolar proteinosis supports the growth of *Mycobacteria*.[18] There is some doubt whether patients in whom these two diseases co-exist can benefit from WLL without increasing the direct risk of transmission.[10] In 1967, a case report of PAP with tuberculosis found that the tuberculosis process did not spread after the second alveolar lavage.[11] A previous study reported that bronchoalveolar lavage in combination with anti-tuberculosis treatment was an effective and safe option for patients with mild PAP patients and tuberculosis.[12] Therapeutic WLL usually re-establishes the macrophage function and decreases the incidence of opportunistic infections.[13] In an 11-year retrospective study in Iran,[27] three of 45 patients with PAP and tuberculosis were cured with anti-tuberculosis therapy, WLL therapy and some treatments the details of which were not described in study. Another single centre study ($n = 9$) of secondary PAP demonstrated that the clinical symptoms and CT findings of four secondary PAP patients secondary to tuberculosis improved after anti-tuberculosis treatment.[28] However, in the two cases, the treatment response was not satisfactory.[28] In one case, although tuberculosis was under control after anti-tuberculosis treatment, PAP progressed rapidly.[10] Another case developed progressive dyspnoea, weakness, cough, fever and chills, and eventually died.[29]

In this current case, the patient did not receive any substantive PAP-related treatment such as WLL, but their condition improved significantly after anti-tuberculous treatment and there was no evidence of recurrence. This indicates the possibility that anti-tuberculosis therapy can improve alveolar proteinosis in PAP patients with secondary *M. tuberculosis* infection. This may be related to the fact that tuberculosis stimulates type II alveolar epithelial cells to secrete excess surfactants, triggering the development of PAP.[30] The findings of another case were consistent with this current case, which showed that treatment for tuberculosis can cause the PAP to partially or totally subside.[31] A cross-sectional study speculated that appropriate antituberculosis therapy may improve outcomes in PAP patients with tuberculosis.[27] Larger studies are warranted to explore the exact relationship between tuberculosis treatment and the prognosis of PAP patients.

Author contributions

Guangtao Fan and Yilong Huang contributed to the case data collection and manuscript preparation. Fenglin Xue contributed to pathological image processing and analysis. Bo He contributed to funding, manuscript preparation and modification.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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