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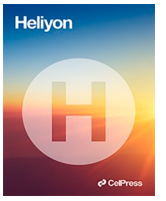

Case report

Silicosis complicated with autoimmune pulmonary alveolar proteinosis caused by long-term dust inhalation during construction of bridge pier columns: A case report

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A R T I C L E I N F O

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A B S T R A C T

Pulmonary alveolar proteinosis (PAP) is characterized by the accumulation of surfactant material in alveoli. Few aPAP cases with a history of dust inhalation show both paves stone-like changes and micronodules in the chest CT scan. We present a 52-year-old male patient withsilicosis complicated with aPAP due to long-term dust inhalation during the construction of bridge piers columns. In this case report, chest CT of the patient displayed nonuniform ground-glass and patchy shadows in both lungs, paving stone-like changes, as well as diffuse distribution of high-density small nodular shadows, and the nodules tended to confluence.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is characterized by the deposition of phospholipid-rich, amorphous, periodic acid-schiff (PAS) stain-positive proteinaceous material in the alveoli and terminal bronchioles, which is a rare chronic lung disease. PAP can be classified into three types: autoimmune PAP (aPAP), secondary PAP (sPAP), and congenital PAP, aPAP accounts for over 90 % of all PAP [1]. The pathogenesis of aPAP is the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies, which leads to the dysfunction of alveolar macrophages and neutrophils, and a decrease in their capacity for removing surfactant, resulting in the accumulation of surfactant within the alveoli [2,3]. Herein, we present a case of 52-year-old male patient with silicosis complicated with aPAP caused by long-term inhalation of dust during construction of bridge pier columns.

2. Case presentation

A 52-year-old man was admitted to our hospital on April 26, 2023. Five years prior to admission, he experienced slight dyspnea after heavier activity, with modified Medical Research Council (mMRC) scale grades of 0–1. He did not receive treatment, and continued working in dusty environments. About 1 year ago, he experienced worsening dyspnea with mMRC grades of 2. Chest CT revealed increased and disordered bilateral lung markings, diffuse distribution of high-density small nodular shadows, nonuniform ground-glass and patchy shadows in both lungs (Fig. 1A). After symptomatic treatment with aminophylline and leaving the dusty environments, his symptoms did not improve. At 4 months ago, he had cough and sputum production, the sputum was white and frothy

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with a small amount. He felt dyspnea during light activity, with an mMRC scale grade of 2–3. His mental status was good, with a weight loss of 2 kg within the last 4 months. He had a 5-year history of hypertension, and orally took amlodipine besylate tablets to control his blood pressure (BP). He had a 35-year smoking history (5 cigarettes per day), engaged in the construction of bridge pier columns for 30 years, and consumed small amounts of alcohol occasionally. He left the dusty environments for more than one year, and now lived at home. He did not have history of contact with poultry, pigeons and mushrooms, and denied a family history of genetic and infectious diseases.

After admission, physical examination showed a temperature of 36.5 °C, a pulse of 90 beats/min, a respiration of 30 beats/min, and a BP of 180/110 mmHg. His height was 167 cm and his weight was 60.0 kg. He had a normal development, moderate nutritional status, and showed clear consciousness, cyanosis, finger clubbing, symmetrical chest expansion, widened intercostal spaces, and shortness of breath. Breath sounds in lungs increased, with crackles being heard in both lungs of the patient. Physical examination of the heart and abdomen was normal. Related auxiliary examinations were performed after admission. Six-minute walk test showed that the patient walked 104 m. Pulmonary function test revealed a predicted/observed forced vital capacity (FVC) of 49 %, predicted/observed forced expiratory volume in 1 s (FEV_1) of 32 %, FEV_1/FVC ratio of 61 %, predicted/observed diffusing capacity of lung for carbon monoxide (DLco) of 38 %. Blood gas analysis (the fraction of inspired oxygen was set to 0.21) showed a PH of 7.44, partial pressure of carbon dioxide (PCO_2) of 36 mmHg, partial pressure of oxygen (PO_2) of 49 mmHg. Liver function test revealed that the lactate dehydrogenase level was 284.30 U/L. Other parameters of liver function test, routine blood tests, rheumatism related tests and pathogenic micro-organisms tests,carcinoembryonic antigen, squamous cell carcinoma antigen, and pro-gastrin-releasing peptide were all normal. The patient had a cytokeratin 19 fragment level of 15.70 ng/mL (normal range <3.3 mg/mL), and neuron-specific enolase level of 22.40 ng/mL (normal range <6.0 ng/mL). Chest CT performed on April 26, 2023 revealed increased and disordered bilateral lung markings, diffuse distribution of high-density small nodular shadows, with a tendency toward confluence of some nodular shadows. Chest CT also showed nonuniform ground-glass and patchy shadows in the lungs, interlobular septal thickening, patency of the trachea and bronchi, cystoid shadow in the right posterior region of the trachea, pleural thickening and adhesion, increased and enlarged hilar and mediastinal lymph nodes with punctate calcification (Fig. 1B).

After admission, the patient underwent bronchoalveolar lavage (BAL), the BAL fluid (BALF) appeared to be colorless and transparent (Fig. 2). Analysis of the differential cell counts in the BALF showed that there were a small number of epithelial cells and inflammatory cells (including 40 % macrophages, 40 % lymphocytes, 15 % neutrophils, and 5 % other cells). Tumor cells were not detected in the BALF. The BALF samples were then subjected to acid-fast staining, fungal smear and culture, bacterial culture, and Xpert *Mycobacterium tuberculosis*/rifampin (MTB/RIF) assay, the results were all negative.

Considering that tumor markers were elevated in the patient, CT-guided percutaneous lung needle biopsy was performed after the consent for biopsy was obtained from the patient and their family members. The hematoxylin and eosin (HE) staining showed a small amount of fibers and the filling of alveolar space with substances (Fig. 3A). Masson's trichrome staining showed a large amount of

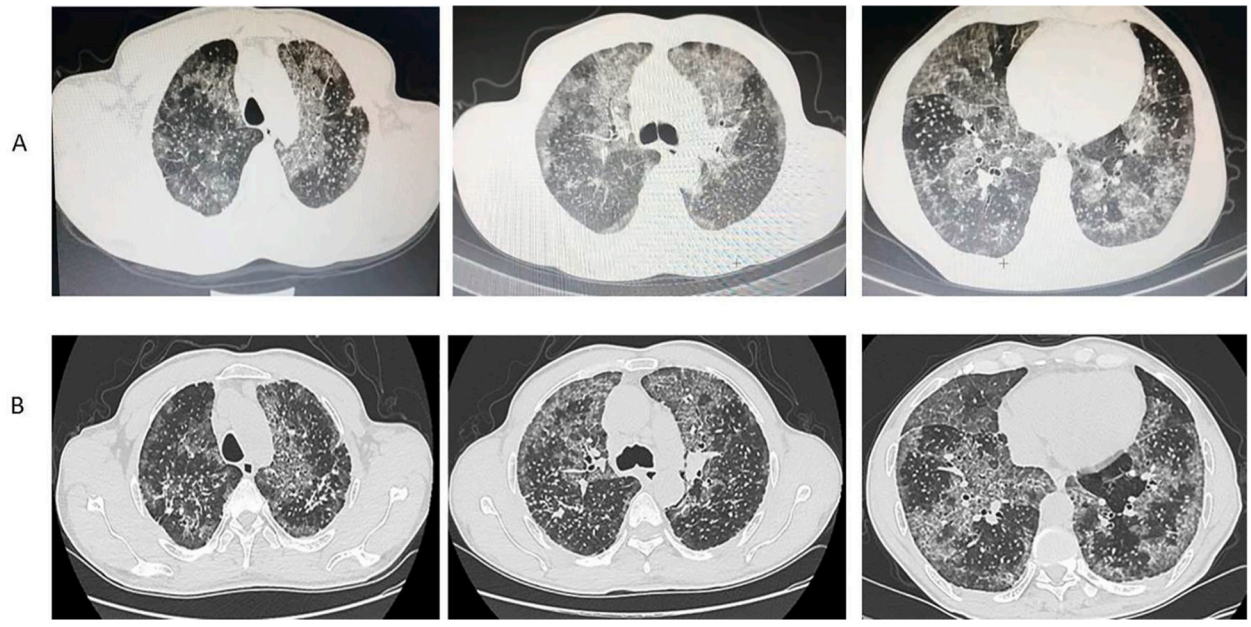

Fig. 1. Chest CT images taken on November 6, 2021 (A) and April 26, 22,023 (B) both revealed diffuse distribution of high-density small nodular shadows in both lungs, with a tendency toward confluence of some small nodular shadows, nonuniform ground-glass and patchy shadows in both lungs, and interlobular septal thickening. Compared with A, B showed a decrease in scattered distributed ground-glass and patchy shadows in both lungs. However, the parameters of the two CT scans are different, which may affect the comparison. Detailed information of A: NMS, neuViz epoch, Kv 120, Thk 1.25mm, matrix size 512 X512; Detailed information of B: Ge medical systems, optima ct680 expert, Kv 120, Thk 0.63mm, matrix size 512 X512.

Fig. 2. The bronchoalveolar lavage fluid obtained from the patient appeared to be colorless and transparent.

collagen fibers deposited around the dust (Fig. 3B). PAS staining reveled the filling of alveolar space with substances that were stained reddish-purple (Fig. 4A). Then PAS-D staining (Fig. 4B1 and B2) was also positive, with a large amount of dust being deposited (Fig. 4B2), suggesting that PAS and PAS-D staining was positive. The serum anti-GM-CSF antibody concentration was 32.4μg/mL (Healthy control was 4.58 μg/mL, the lower detection limit was 1.0 pg/mL. Quanzhou jiubang Biotechnology Co., Ltd, China). The BALF were submitted to determine the components of the dust, the results revealed that high contents of silicon, small amounts of iron, bromine, aluminum, magnesium and calcium were seen in the BALF.

The patient were diagnosed with silicosis complicated with aPAP, and was advised to undergo whole lung lavage and inhaled GM-CSF treatment. He eventually refused treatment due to the high cost of treatment. He felt cough and during light activity were the same as before. At present, he was on long-term home oxygen therapy and took aminophylline and the mMRC scale grades was still 2 intermittently by the phone call following-up on September 01, 2024.

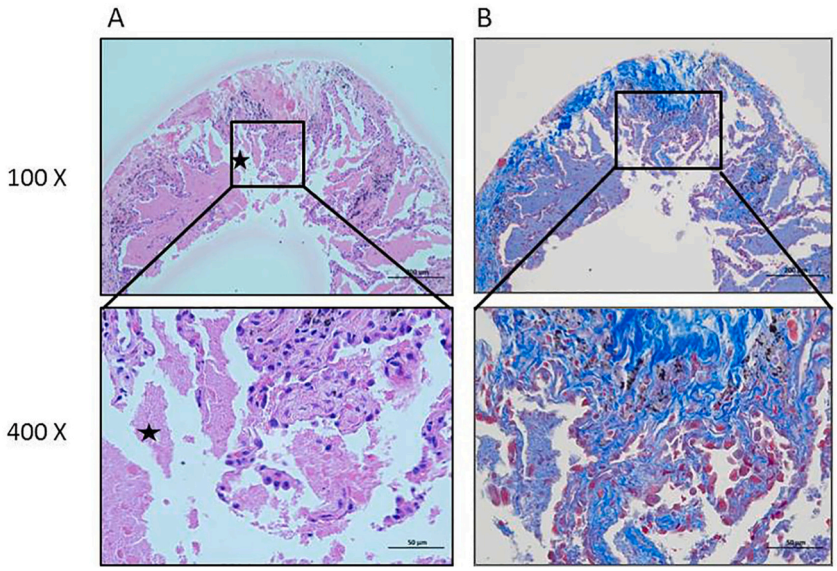

Fig. 3. Pathological results. A: The hematoxylin and eosin (HE) staining showed a small amount of fibers and obvious alveolar epithelial hyperplasia and the alveolar space was filled with substances that were stained eosinophilic (Black star). B: Masson's trichrome staining showed a large amount of collagen fibers deposited around the dust.

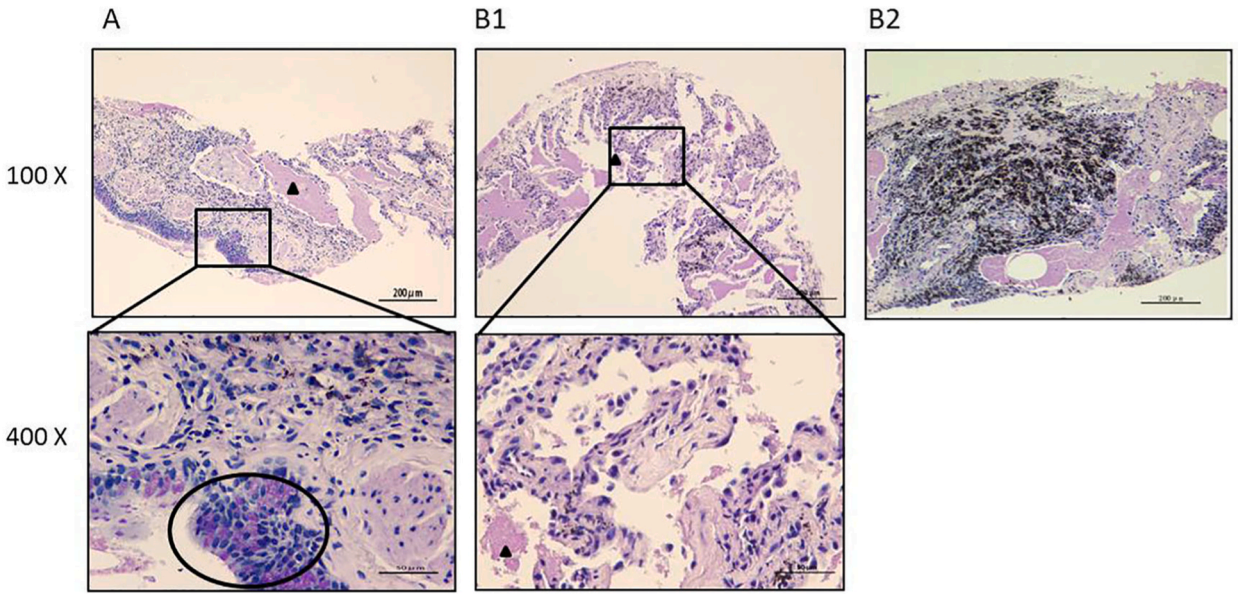

Fig. 4. PAS and PAS-D staining results. A: Periodic Acid-Schiff (PAS) staining reveled the filling of alveolar space with substances that were stained reddish-purple (Black triangle), and PAS-positive goblet cells (Black circle). B1 and B2: Periodic Acid-Schiff Diastase (PAS-D) reveled the filling of alveolar space with substances that were stained reddish-purple (Black triangle), with a large amount of dust being deposited (Fig. 4B2).

3. Discussion

Using the Poisson distribution, the incidence and prevalence of aPAP was about 1.65 and 26.6 per million, respectively [4]. It has been found that approximately 23 %–32 % of aPAP patients have a history of dust inhalation [5,6], and 72 % of the patients have a smoking history [7]. Although smoking is a suspected risk factor for aPAP, a previous study showed that the serum GM-CSF antibody levels were not related to sex, smoking status, history of occupational dust inhalation, and concurrent diseases, and the serum GM-CSF antibody concentration s in aPAP patients was markedly higher than that in healthy controls and other diffuse interstitial lung diseases [5]. And another study reported that among 17 aPAP patients having a history of occupational dust exposure, 13 patients were positive for GM-CSF antibodies, and 10 out of the 17 patients were exposed to silica dust, of the 10 patients, 6 patients had positive serum GM-CSF antibodies [6].

A previous study [6] reported that among 13 aPAP patients with a history of occupational dust exposure, only paving stone-like changes were found in 11 patients, and only micronodules were noted in 2 patients. CT scans of almost all aPAP patients showed that the most common abnormality was ground-glass opacity; the second was interlobular/intralobular septal thickening, which was characterized by typical paving stone changes or map changes [8]. Silicosis is divided into acute and chronic silicosis. Acute silicosis differs greatly from chronic silicosis in its pathological features and resembles primary alveolar proteinosis, referred to herein as silicosis. In comparison to chronic classic silicosis characterized by chronic and often asymptomatic pulmonary disease after decades of exposure, acute silicosis manifests rapidly progressive respiratory failure. As previously reported, the most common finding on CT scans of silicoproteinosis (12 of 13 patients, 92 %) was air space consolidation [9]. While chest radiographs of a patient with chronic classic silicosis included simple nodular silicosis and progressive massive fibrosis. CT scan of simple nodular silicosis was characterized by many nodules of varying sizes [10]. Generally, BALF obtained from patients with aPAP after dust inhalation typically had an milky white and muddy appearance, only one case report found that BALF of aPAP after exposure to a fire extinguisher containing silica powder was colorless and transparent [11,12]. APAP can be caused by variety of occupational inhalation exposures, silica is the most frequently reported exposures [13–15]. Intratracheal instillation of silica in rats can increase the synthesis and secretion of surfactant by alveolar type II cells, leading to impaired surfactant clearance [15,16]. In terms of iron, iron homeostasis is found to be disrupted in patients with PAP. Hemosiderin-laden macrophages in lung tissues containlots of iron [17,18]. In this case report, the patient engaged in the construction of bridge pier columns for 30 years, without progressive respiratory failure in the last 2 years. The BALF obtained from the patient had high contents of silicon, small amounts of iron, and he was positive for serum GM-CSF antibodies. HE and MASSON staining showed accumulation of dust particles and hyperplasia of peripheral fibers, both PAS and PAS-D staining were positive. And chest CT of the patient displayed both paving stone-like changes, and diffuse distribution of high-density small nodular shadows. Therefore, this patient was diagnosed as rather aPAP superimposed on chronic silicosis than acute silicosis (silicoproteinosis). We speculated that the occurrence of aPAP and chronic silicosis in the patient may be caused by inhalation of silicon.

The whole-lung lavage and inhaled GM-CSF therapy are the main treatment methods for aPAP [7,19,20]. A 10-year follow-up study showed that among 21 asymptomatic patients with PAP who did not receive whole-lung lavage or inhaled GM-CSF therapy, the condition of 4 (28.2 %) patients improved, 15 patients had no change, and only 2 patients worsened [5], lung lesions may be absorbed in patients after leaving the dusty environments [5,10]. In this case report, the patient did not receive these treatments due to excessive

financial burden. The patient was removed from the dusty environments and lived at home about one year ago. In comparison with the chest CT image (Fig. 1A) taken one year ago, the chest CT image (Fig. 1B) taken in our hospital showed a decrease in ground-glass shadows in both lungs. we predicted the patient's ground-glass shadows of chest CT improvement was due to escape from dusty environments. However, the parameters of the two CT scans are different, which may affect the comparison. We will continue to follow up.

Although previous studies found that more than 25 % of aPAP patients have a history of dust inhalation. The main differences between this patient and the previous patients with chronic dust inhalation were image findings and BALF appearance. The imaging findings of this patient were more complicated than previously reported, and BALF was atypical, which was easy to be misdiagnosed clinically. Ultimately, the diagnosis was confirmed according to HE staning and Masson's trichrome staining of the biopsy samples and medical history and imaging features.

CRediT authorship contribution statement

Jie Jiang: Writing – original draft, Data curation. **YouMing Zhu:** Data curation. **Tao Jiang:** Methodology. **TingTing Hu:** Data curation. **YiLing Gan:** Writing – review & editing, Methodology, Funding acquisition.

Data availability statement

Data are available upon direct request.

Ethics statement

This study was approved by the Ethics Committee of our hospital, and written informed consent was obtained from the patient.

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Declaration of competing interest

The authors declare that they have no competing interests.

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