Pulmonary alveolar proteinosis and occupational exposure: Case analysis

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ABSTRACT

Pulmonary alveolar proteinosis (PAP), an extremely rare disease, is potentially caused by occupational exposure. Identifying the occupational etiology may help to avoid recurrence of the disease by refraining from further work exposure. In this study, PAP cases with pathological confirmation in a tertiary medical center diagnosed between 1995 and 2006 were identified through a review of medical records. A descriptive analysis of relevant characteristics was carried out and the relationship between PAP and occupational exposure was explored. In total, three male and two female patients were identified. Dyspnea on exertion and a cough were the main symptoms. Bronchoalveolar lavage was performed in all patients and proved to be an effective treatment. Two men were exposed to silica sand at work. One was a foundry worker who became ill after 20 years of work, and two of his coworkers presented with similar symptoms. The other male patient was a sandblaster who developed symptoms within three months of starting work. As silica-like birefringent substances were found in the lung tissues of these two men, their PAP was highly suspected to be work-related. As for the other three patients, significant exposure could not be identified either at work or at home. The causes of their diseases remained unclear. In conclusion, occupational exposure is one possible cause of PAP. A detailed occupational history helps to identify potential causes and to avoid further exposure, so that recurrence of the disease can be prevented.
Introduction

Pulmonary alveolar proteinosis (PAP) was first described by Rosen et al. [1] in 1958. It is characterized by the accumulation of periodic acid Schiff (PAS)-positive phospholipoproteinaceous materials as surfactants in the alveoli, resulting in impaired gas exchange and respiratory difficulty [2]. PAP presents in three clinically distinct forms: congenital, idiopathic and secondary PAP. Congenital PAP (2%) is believed to be caused by mutations in the genes encoding the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor and presents as neonatal respiratory distress syndrome [2-5]. Idiopathic PAP, which accounts for the majority of PAP cases (90%), is associated with the GM-CSF autoantibody, which inhibits the alveolar macrophage function [2,3,5]. Finally, secondary PAP (5 ~ 10%) is related to abnormal alveolar macrophage function due to hematologic disorders, infections, immunosuppression or toxic exposure such as exposure to silica [2,4-6]. Bronchoalveolar lavage (BAL) is the standard treatment for PAP [2]. In cases of secondary PAP, definitive treatment also relies on treating the underlying diseases or avoiding further toxic exposure [4]. Nevertheless, it is usually difficult to establish the relationship between toxic exposure and PAP.

This study analyzed PAP cases in a tertiary medical center retrospectively. A detailed occupational history was obtained in order to explore the relationship between PAP and occupational exposure, in conjunction with a review of relevant literature.

Methods

Possible cases of PAP in the period of 1995 ~ 2006 were identified through a review of inpatient discharge data and outpatient data in a tertiary medical center in central Taiwan, using ICD-9 code 516.0. Eligible cases were confirmed to be true PAP by pathologic reports. Clinical features, occupational and environmental histories, and follow-up information were retrieved from medical charts and through interviews. Lacking quantitative dust measurements, the intensity of exposure to suspicious agents was estimated from patients’ statements and reviews of relevant literature regarding working conditions [7-9]. A descriptive analysis of patient characteristics was carried out and the relationship between PAP and occupational exposure was explored. The Institutional Review Board of Changhua Christian Hospital approved the study (CCH:070201) and informed consent was obtained from each patient.

Results

Clinical summaries

In total, five patients were confirmed as PAP cases. The clinical data are summarized in Table 1. The histological features showed almost complete filling of alveolar spaces and terminal bronchioles with PAS-positive eosinophilic proteinaceous granular materials. The alveolar architecture was well-preserved (Figure 1A). Polarized light microscopy images showed numerous birefringent substances in patients A and B (Figure 1B), some in patient D, and none in patients C and E.

Clinically, dyspnea on exertion was the most common symptom, followed by other symptoms ranging from mild sputum only (patient D) to severe respiratory failure (patient A). Radiographic patterns showed bilateral air-space consolidation (Figure 2) in four patients, while a solitary nodule was found in the other patient. High-resolution computed tomography (HRCT) revealed geographic, patchy, ground-glass opacification with interlobular septal thickening, a pattern referred to as “crazy paving” (Figure 3).

Bronchoalveolar lavage (BAL) was performed in all five patients, all of which experienced clinical and radiographic improvement following BAL. BAL was repeated in two patients on account of disease recurrence. All patients remained stable during the follow-up period.

Occupational and environmental exposure

Patient A: This 48-year-old man had worked in a copper foundry for more than 20 years before PAP was diagnosed. In the first ten years, he
performed sand molding in a 4.5 m × 15 m × 4 m room. A large roll-up door provided the only ventilation. He worked for eight hours a day, five to six days a week. Later, he became the owner of a foundry, where all the tasks, e.g., sand molding, copper melting, and die casting, were performed in a 16 m × 16 m × 8 m room. A large door (3.6 m × 3 m) and eight small windows provided natural ventilation. There was no exhaust ventilation system in place. Each day he spent four hours around the furnace, and the rest of the time he delivered goods. Both furnace operation and sand molding generated visible fumes and silica-containing dust, but he did not wear any masks. At the end of each shift, his nostrils were described as being coated with white dust. The workload and working conditions did not change during the period prior to disease onset. The patient left his job after becoming ill with PAP. Coincidentally, a colleague quitted the job on account of suffering a cough and dyspnea a few months before our patient became ill. Moreover, the patient’s uncle developed respiratory symptoms months afterwards. The two people experienced similar working conditions to our patient, but their clinical diagnoses were not available.

**Patient B:** This 33-year-old man had been a sandblaster of rusty steel for three months when PAP was diagnosed. Before starting this work,
he was an oil tank driver for eight years, and no discomfort had been noted during this period of time. His sandblasting workplace appeared so dusty that his skin and clothes were coated with silica dust at the end of the shift. At work, he wore only a simple charcoal mask. Exertional dyspnea was noted within three months of starting this new job. No other sources of exposure to dust or chemicals could be identified. After discharge from hospital, he reverted back to being a truck driver.

**Patient C:** This 47-year-old man had worked in a wine factory for 24 years when PAP was diagnosed. He operated wine-filling machines. A smell of alcohol and particles of cork were present in the air. Otherwise, no chemical or dust exposure could be identified at work or outside the workplace.

**Patient D:** This 46-year-old woman was a housewife. She denied any chemical or dust exposure in her house and the surrounding environment.

**Patient E:** This 47-year-old woman was a housewife who started to work as a rice noodle maker at age 38. She was responsible for mixing flour and cooking rice noodles. The working environment was hot and humid, but not dusty. She did not wear a mask at work. No other chemical or dust exposure could be identified in the workplace or at home. Concerned about further progression of the disease, she left the job after the last relapse of PAP.

A summary of the occupational exposures and indices of causality is presented in Table 2.

**Discussion**

Progressive exertional dyspnea and a dry cough are the most common symptoms of PAP, accompanied by restrictive deficits in pulmonary function tests [4,10]. The clinical severity may range from spontaneous recovery to death from pneumonia or respiratory failure [11]. Chest radiography features bilateral central and symmetric alveolar infiltration with relative sparing of apices and costophrenic angles [4]. The opacities may be of the form of a ground-glass appearance, reticulonodular infiltration, or consolidation [4]. The absence of cardiomegaly differentiates this disease from cardiogenic pulmonary edema [12]. “Crazy-paving,” though neither specific nor sensitive, is a typical pattern of PAP in HRCT, which shows ground-glass opacity with superimposed interlobular septal thickness adjacent to normal lung parenchyma [4,5]. The gold standard for diagnosing PAP is open-lung
Table 2. Exposure history and indices of occupational causality in the 5 cases of pulmonary alveolar proteinosis (PAP)

<table>
<thead>
<tr>
<th>Causality</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
<th>Patient D</th>
<th>Patient E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suspicious agent in the workplace</td>
<td>Silica dust</td>
<td>Silica dust</td>
<td>Cork dust</td>
<td>None</td>
<td>Flour dust</td>
</tr>
<tr>
<td>2. Estimated exposure dosage /duration</td>
<td>Significant/20 years</td>
<td>Significant/3 months</td>
<td>Some but not relevant/24 years</td>
<td>None</td>
<td>Some but not relevant/9 years</td>
</tr>
<tr>
<td>3. Literature evidence of a link with PAP</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>--</td>
<td>No</td>
</tr>
<tr>
<td>4. Histopathological/mineralogical evidence in lung tissues</td>
<td>PAP with a large amount of birefringent substances. Silicotic nodule(-)</td>
<td>PAP with a large amount of birefringent substances. Silicotic nodule(-)</td>
<td>PAP without any particle identified.</td>
<td>PAP with a few birefringent substances. Silicotic nodule(-)</td>
<td>PAP without any particle identified.</td>
</tr>
<tr>
<td>5. Clinical improvement following removal from work exposure</td>
<td>Yes</td>
<td>Yes</td>
<td>Did not change working pattern</td>
<td>--</td>
<td>Yes</td>
</tr>
<tr>
<td>6. Co-workers with similar symptoms or disease</td>
<td>Possibly two coworkers</td>
<td>Unknown</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7. Other predisposing factors for PAP</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Other predisposing factors for PAP include hematologic disorders, infections, immunosuppression or toxic exposure (e.g., aluminum dust, titanium dioxide, cellulose fibers, etc.).
biopsy [3], but BAL alone suffices in most cases nowadays [6,13]. In our cases, the clinical pictures, radiographic features and histopathologic findings were compatible with PAP.

Pulmonary alveolar proteinosis is a rare disease, with only five confirmed patients in 12 years in the tertiary medical center. The estimated prevalence ranged from 1.0 to 6.2 cases per million people in previous studies [2-4]. It is so rare that most physicians are unfamiliar with it, and diagnosis may therefore be delayed [11]. In addition, possible etiologies might not be identified. Occupational or environmental exposure is the cause of PAP in some cases [4,5]. In such toxic cases, BAL is therapeutically effective, but the most important management to prevent disease recurrence is to cease exposure [14].

To diagnose occupational PAP, several elements must be taken into consideration. First, a detailed occupational history has to be obtained in order to pinpoint potential exposure to offending agents [14]. Second, the intensity and duration of exposure, as well as the temporal relationship between employment and disease, must be evaluated. Third, scientific literature regarding the link between suspected agents and PAP must be reviewed. For example, free crystalline silica [12,14,15], aluminum dust [16], titanium dioxide [17], and cellulose fibers from home insulation materials [18] have been reported to cause PAP. Fourth, there should be a search for offending agents in biological tissues by adequate laboratory techniques. For example, McCunney and Godefroi [15] discovered an increased number of silicon particles in lung tissues of PAP patients using electron dispersive spectroscopy. Miller et al. [16] observed more than 300 million particles of aluminum per gram of dry lung tissue by a combination of morphology, electron diffraction, and energy dispersive X-ray spectroscopy. Fifth, one must assess whether the disease improves after removal from work exposure. Such an improvement is confirmatory of an occupational origin of PAP.

Sixth, one must inquire as to the presence of similar symptoms among co-workers. A surveillance of suspected workplaces should be considered. Finally, one must rule out other known associated disorders of PAP, such as hematological disorders, infections, immunosuppression or toxic exposure.

In our study, dust exposure in the workplace could be traced in patients A, B, C, and E, but not in patient D. The exposure was to silica sand in patients A and B, cork dust in patient C, and flour dust in patient E. Some studies [6,12,14,15] have proved that silica is a possible cause of PAP, but not cork dust or flour dust. Besides, no special particles were found in the lung tissues of patients C or E. In all five patients, no other conditions such as hematological disorders or infections associated with PAP were found. In summary, patients C, D and E seem to have presented with idiopathic PAP, whereas patients A and B are likely to be cases of occupational PAP.

Both patients A and B were occupationally exposed to silica sand containing free crystalline silica, which has been proved to be a possible cause of PAP in previous studies [6,12,14,15]. Patient A was exposed to silica continuously for more than 20 years in a foundry. Cumulative exposure and the temporal sequence of his history may be compatible with silica-related PAP. Research in Taiwan [8,9] has revealed dust exposure in the range of 0.142 mg/m$^3$ to 37 mg/m$^3$, with as many as 58.5% of samples exceeding the PEL-TWA (permissible exposure limit, time-weighted average, defined for silica content > 10%) set by the Taiwanese Occupational Safety and Health Administration. The factory that patient A worked in, according to our on-site walk-through, was typical and similar to those described in the cited domestic literature [8,9]. Moreover, two coworkers of patient A quitted the job on account of suffering a cough and dyspnea. A diagnosis of PAP was not confirmed, but this fact implied poor working conditions and a speculative speculation of significant exposure. Patient B was a sandblaster for only three months. Sandblasting is the most common cause of acute silicoproteinosis. Samimi et al. [7] reported that within fewer than 2½ hours of sandblasting, the average concentration of crystalline silica was...
764 micrograms per cubic meter (μg/m³), which is twice the PEL-TWA. The higher the silica content in the dust, the more toxic the exposure will be. Exposure to a high concentration of silica could cause symptoms of acute silicoproteinosis within weeks [19]. Furthermore, silica sand used in sandblasting usually fractures into fine particles, and freshly crushed silica is believed to evoke a more severe lung reaction than aged silica [20]. The exposure to freshly crushed silica during sandblasting without adequate respiratory protection may explain the rapid clinical course of patient B. In both patients A and B, large amounts of silica-like birefringent materials were found in the lung tissues. Their clinical conditions improved after BAL and remained stable after refraining from further exposure. Finally, no other predisposing factors associated with PAP such as hematological disorders or infections were identified in both patients. All the evidence supported the diagnosis of occupational PAP. On the other hand, PAP in patients C, D, and E could not be attributed to external exposure. Cork and flour dusts haven’t been shown to be related to PAP, while patient D did not experience any obvious exposure. These cases may well be categorized as idiopathic PAP.

In conclusion, occupational exposure is one possible etiology of PAP. Based on occupational and environmental histories, clinical manifestations, radiological features, histopathological findings, and a literature review, it is possible that in two patients (A and B) in our series, PAP was causally related to silica dust exposure in the workplace. Once occupational disease is suspected, effort must be made to eliminate workplace exposure through engineering control, general or local exhaust ventilation, or the use of personal protective equipment. This study emphasizes the importance of obtaining a detailed occupational history for the identification and management of PAP.

References


