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Secondary Pulmonary Alveolar Proteinosis Associated with Aluminum Exposure：a Case Report and Literature Review

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Case Report

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by abnormal accumulation of surfactant-derived material within the alveoli. Occupational exposure-related secondary PAP is uncommon, and aluminum dust represents one of the recognized metallic exposures associated with this condition, although reported cases remain limited.

A 45-year-old man presented with progressive dyspnea, hypoxemic respiratory failure, and diffuse bilateral ground-glass opacities. Extensive infectious and autoimmune investigations were negative. Bronchoalveolar lavage fluid (BALF) appeared characteristically milky with abundant sediment. Histopathological and cytological examinations demonstrated intra-alveolar proteinaceous material with positive periodic acid-Schiff (PAS) and diastase-resistant PAS staining. Anti-granulocyte–macrophage colony-stimulating factor (GM-CSF) antibodies were negative (3.25 U/mL). Detailed occupational history revealed recent employment involving aluminum spraying and electric welding. Quantitative elemental analysis demonstrated markedly elevated aluminum concentrations in BALF (1473.6μg/L versus 103μg/L in healthy controls) and workplace welding residues (6011.8 μg/L). Sequential bilateral whole-lung lavage resulted in significant clinical and radiological improvement.

This case demonstrates a comprehensive exposure–deposition evidence chain linking occupational aluminum-containing welding fumes, elevated aluminum concentrations in workplace residues and bronchoalveolar lavage fluid, and the development of secondary PAP. This case highlights that occupational aluminum exposure may present as secondary PAP rather than classical pneumoconiosis alone. Clinicians should maintain a high index of suspicion for occupational PAP in patients with unexplained diffuse pulmonary infiltrates and a relevant exposure history.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the accumulation of surfactant-derived lipoproteinaceous material within the alveoli due to impaired surfactant clearance by alveolar macrophages [1–3]. Based on the underlying pathogenesis, PAP is classified into autoimmune, secondary, and congenital forms, with autoimmune PAP accounting for approximately 90% of adult cases [2, 3]. Secondary PAP (sPAP) occurs in association with hematologic disorders, malignancies, infections, immunodeficiency, or inhalational exposure to toxic particles that impair alveolar macrophage function [2, 3].

Occupational exposure-related sPAP is uncommon but has been reported following exposure to silica, indium-tin oxide, and other inorganic particles [4, 5]. Aluminum-associated sPAP remains exceptionally rare, and most published cases have relied primarily on occupational history or tissue elemental analysis to support the diagnosis [6, 7]. Here, we report a patient with secondary PAP following occupational exposure to aluminum-containing welding fumes. Quantitative aluminum analysis demonstrated markedly elevated aluminum concentrations in both bronchoalveolar lavage fluid (BALF) and workplace

welding residues, providing complementary biological and environmental evidence supporting an occupational exposure-related etiology.

2. Case Presentation

A 45-year-old man was admitted to our hospital with progressive exertional dyspnea, chest tightness, and hypoxemic respiratory failure for more than three months. His symptoms began in January 2026 following an upper respiratory tract infection and gradually worsened despite multiple courses of antimicrobial therapy and systemic corticosteroids.

The patient had no history of chronic lung disease, smoking, autoimmune disease, or hematological disorders. He had worked as a steel structure worker for more than 20 years. From August to November 2025, he was employed at a bridge-component manufacturing factory, where his duties included aluminum spraying and electric welding. During this period, he was regularly exposed to metal-containing aerosols and welding fumes. Although he routinely wore a disposable dust mask and face shield during work, no powered air-purifying respirator or specialized respiratory protective equipment was used.

On admission, the patient presented with type I respiratory failure requiring high-flow nasal cannula (HFNC) support with a fraction of inspired oxygen (FiO_2) of 45% at a flow rate of 45 L/min. His respiratory rate was 30 breaths/min, heart rate 110 beats/min, and oxygen saturation on room air was 86%. Physical examination revealed orthopnea, tachypnea with accessory respiratory muscle use, and bilateral fine Velcro crackles on lung auscultation. No digital clubbing or peripheral edema was observed. Owing to severe hypoxemia and respiratory distress, pulmonary function testing could not be performed at presentation.

High-resolution chest computed tomography (HRCT) demonstrated diffuse bilateral ground-glass opacities with mosaic attenuation and multifocal subpleural consolidative lesions (Fig. 1).

Flexible bronchoscopy revealed characteristic milky bronchoalveolar lavage fluid (BALF) with abundant proteinaceous sediment (Fig. 2A). Cytological examination demonstrated abundant eosinophilic proteinaceous material without evidence of malignancy. Transbronchial lung biopsy showed alveolar epithelial hyperplasia with abundant intra-alveolar eosinophilic material. Following repeat pathological review, periodic acid–Schiff (PAS) and diastase-resistant PAS (D-PAS) staining remained strongly positive, confirming the presence of surfactant-derived proteinaceous material characteristic of pulmonary alveolar proteinosis (Fig. 3).

Autoimmune PAP was considered initially. Serum anti-granulocyte–macrophage colony-stimulating factor (GM-CSF) antibody measured by chemiluminescence immunoassay was below conventional cutoff (3.25 U/mL, cutoff 20 U/mL). To identify the underlying cause of secondary PAP, extensive investigations were performed. Repeated microbiological examinations, including bacterial, fungal, viral, mycobacterial, and *Pneumocystis jirovecii* testing, were all negative. Autoimmune serology and

hematological evaluation revealed no evidence of connective tissue disease, hematologic malignancy, or immunodeficiency. Considering the close temporal relationship between occupational metal exposure and disease onset, occupational exposure-related secondary PAP was strongly suspected.

To further investigate pulmonary metal deposition, transbronchial lung biopsy specimens underwent scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM-EDS). Multiple metallic elements were detected across the analyzed regions. Aluminum was detected at all sampling sites, ranging from 0.4 to 3.3 wt.%. Indium showed a heterogeneous distribution, ranging from undetectable levels to 12.2 wt.%, whereas tin was detected at all sampling sites and ranged from 1.0 to 17.5 wt.%, with relatively high concentrations in several regions. Titanium was detected only in two sampling sites (3.0 and 6.7 wt.%), while gallium was present at low levels (0.7–2.2 wt.%). Quantitative elemental analysis using inductively coupled plasma mass spectrometry (ICP-MS) subsequently demonstrated a markedly elevated aluminum concentration in BALF (1473.6 μg/L) compared with non-PAP controls (103 μg/L), and workplace welding residues contained 6011.8 μg/g aluminum. In contrast, indium and tin were not detected in either BALF or workplace samples. Taken together with the patient's documented history of aluminum spraying immediately preceding disease onset, these findings suggested aluminum as the predominant identifiable occupational exposure associated with the development of PAP, although previous or mixed-metal exposure could not be completely excluded.

Based on the characteristic BALF appearance, typical pathological findings, negative anti-GM-CSF antibody, exclusion of alternative causes of secondary PAP, detailed occupational exposure history, and elemental analyses, the patient was diagnosed with secondary pulmonary alveolar proteinosis associated with occupational metal exposure, most likely related to aluminum-containing welding fumes.

The patient initially received systemic corticosteroid therapy together with inhaled granulocyte–macrophage colony-stimulating factor (GM-CSF). However, respiratory symptoms and hypoxemia showed little improvement, and follow-up imaging demonstrated persistent diffuse pulmonary infiltrates. Because of progressive respiratory failure despite medical treatment, sequential bilateral whole-lung lavage (WLL) was subsequently performed (Fig. 2B). The patient's dyspnea and oxygenation improved markedly after treatment, and follow-up HRCT demonstrated substantial resolution of bilateral pulmonary infiltrates (Fig. 1). Corticosteroids were gradually tapered.

Following stabilization of respiratory status, pulmonary function testing, which had been impossible to perform at admission, demonstrated a moderate restrictive ventilatory defect with severely impaired gas transfer (FVC 57% predicted, FEV_1 56% predicted, TLC 56% predicted, and DLCO 32% predicted). At the 3-month follow-up, the patient was able to ambulate approximately 500 m during daily activities while receiving supplemental oxygen at 2 L/min via a portable oxygen concentrator, representing a marked improvement in functional capacity compared with presentation.

3. Discussion

Secondary pulmonary alveolar proteinosis (sPAP) is a rare subtype of PAP resulting from impaired alveolar macrophage function secondary to hematologic disorders, infections, malignancies, or inhalational exposures [2, 3]. Occupational exposure to inorganic dusts and metal-containing aerosols is an increasingly recognized cause of sPAP, although aluminum-associated cases remain exceptionally uncommon [4–6].

Several findings supported the diagnosis of sPAP in our patient. Characteristic milky bronchoalveolar lavage fluid, positive PAS and diastase-resistant PAS staining, and negative anti-GM-CSF antibodies effectively excluded autoimmune PAP. In addition, extensive microbiological and autoimmune investigations were unrevealing, making infectious or connective tissue disease-associated diffuse lung disease unlikely.

Occupational exposure appeared to play a central role in disease development. The patient had recently performed aluminum spraying and electric welding in a bridge-component manufacturing factory before symptom onset. SEM-EDS identified aluminum, indium, and tin within lung tissue, indicating previous exposure to multiple metallic particles. However, quantitative ICP-MS analysis detected markedly elevated aluminum concentrations in BALF and workplace residues, whereas indium and tin were not detected in these samples. Although previous occupational exposure to indium- or tin-containing materials cannot be completely excluded, the close temporal relationship between aluminum spraying and symptom onset, together with the environmental and biological aluminum measurements, suggests that aluminum-containing dust was the predominant exposure associated with disease development. This case also highlights that occupational metal-related sPAP may result from complex mixed-metal exposure and that comprehensive elemental analysis should not be limited to a single metal.

An important strength of this case is the establishment of a comprehensive exposure–deposition evidence chain. Previous reports of aluminum-associated PAP relied primarily on occupational history or tissue elemental analysis to support causality [5, 6]. In contrast, our patient underwent quantitative aluminum measurements in both BALF and workplace welding residues, providing complementary biological and environmental evidence linking occupational exposure to disease development. To our knowledge, few published reports have incorporated both BALF elemental analysis and workplace environmental measurements when evaluating aluminum-associated sPAP.

Only a limited number of aluminum-associated PAP cases have been reported. Miller et al. first described PAP in an aluminum rail grinder and demonstrated extensive pulmonary aluminum deposition [5]. More recently, Chew et al. reported PAP in a boilermaker with prolonged occupational aluminum exposure, in whom elemental analysis confirmed aluminum accumulation in lung tissue and mediastinal lymph nodes [6]. Compared with these reports, our case provides additional quantitative evidence by demonstrating elevated aluminum concentrations in both BALF and workplace residues (Table 1).

The exact mechanisms underlying aluminum-associated PAP remain incompletely understood. Current evidence suggests that inhaled metal particles impair alveolar macrophage function, resulting in defective surfactant clearance and progressive accumulation of lipoproteinaceous material within the

alveoli [2, 3]. Because welding fumes contain multiple metallic particles, the contribution of other inhaled metals cannot be completely excluded. Nevertheless, aluminum was consistently identified in workplace residues, BALF, and lung tissue, supporting its role as the predominant occupational exposure in the present case.

Whole-lung lavage (WLL) remains the standard treatment for symptomatic PAP [8]. Following sequential bilateral WLL, our patient demonstrated marked improvement in respiratory symptoms, oxygenation, and radiological abnormalities, further supporting the diagnosis.

This report has several limitations. First, quantitative aluminum burden was not measured directly in lung tissue. Second, welding fumes contain multiple metallic components, making it difficult to attribute disease solely to aluminum exposure. Finally, this is a single case, and causality cannot be definitively established.

In conclusion, we report a rare case of secondary PAP associated with occupational exposure to aluminum-containing welding fumes. Quantitative aluminum analysis of both BALF and workplace welding residues, together with pathological findings and clinical response to WLL, established a comprehensive exposure–deposition evidence chain supporting an occupational exposure-related etiology. Our findings highlight the value of integrating occupational history with biological and environmental elemental analyses in the evaluation of suspected secondary PAP.

Table 1
Published cases of aluminum-associated secondary pulmonary alveolar proteinosis

Study	Occupation	Aluminum exposure	Diagnostic evidence	Anti-GM-CSF	Treatment	Outcome
Miller et al., 1984	Aluminum rail grinder	Aluminum dust	Lung tissue aluminum deposition	Not Reported	Whole-lung lavage	Improved
Chew et al., 2016	Boilermaker / boat builder	Aluminum dust	Lung tissue and mediastinal lymph node aluminum	Not Reported	Whole-lung lavage	Improved
Present case	Bridge-component worker	Aluminum spraying and welding fumes	BALF aluminum (1473.6 μg/L), workplace residue aluminum (6011.8 μg/L), SEM-EDS	Negative (3.25 U/mL)	Sequential whole-lung lavage	Improved

Abbreviations

BALF
bronchoalveolar lavage fluid

D-PAS
diastase-resistant periodic acid–Schiff
GM-CSF
granulocyte–macrophage colony-stimulating factor
HFNC
high-flow nasal cannula
HRCT
high-resolution computed tomography
ICP-MS
inductively coupled plasma mass spectrometry
PAP
pulmonary alveolar proteinosis
PAS
periodic acid–Schiff
SEM-EDS
scanning electron microscopy with energy-dispersive X-ray spectroscopy
sPAP
secondary pulmonary alveolar proteinosis
WLL
whole-lung lavage.

Declarations

Ethics approval and consent to participate

This study was granted an exemption from ethical review by the Institutional Review Board of Peking Union Medical College Hospital. Written informed consent was obtained from the patient for participation in this study.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Y.L. drafted the manuscript and collected the clinical specimens. J.Z. and R.Z. performed and interpreted the pathological and elemental analyses. F.W. and J.L. contributed to specimen collection. B.C. contributed to specimen analysis. X.T. and X.S. supervised the study. J.Z. contributed to the clinical management and data collection. C.S. supervised the study and critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

References

1. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med. 1958;258:1123–42.
2. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med. 2002;166(2):215–35.
3. Trapnell BC, Nakata K, Bonella F, et al. Pulmonary alveolar proteinosis. N Engl J Med. 2023;389:54–65.
4. Cummings KJ, Donat WE, Ettensohn DB, Roggli VL, Ingham CB, Kreiss K. Pulmonary alveolar proteinosis in workers at an indium processing facility. Am J Respir Crit Care Med. 2010;181(5):458–64.
5. Miller RR, Churg AM, Hutcheon M, Lam S. Pulmonary alveolar proteinosis and aluminum dust exposure. Am Rev Respir Dis. 1984;130(2):312–5.

6. Chew R, Golledge C, Bryant DH. Alveolar proteinosis associated with aluminium dust inhalation. Occup Med (Lond). 2016;66(6):492–4.
7. Huaringa AJ, Francis WH, Chui C, Carbajal JR. Pulmonary alveolar proteinosis: a case report and world literature review. Clin Case Rep. 2016;4(12):1115–9.
8. Campo I, Mariani F, Paracchini E, et al. Pulmonary alveolar proteinosis: diagnostic and therapeutic challenges. Multidiscip Respir Med. 2012;7:4.

Figures

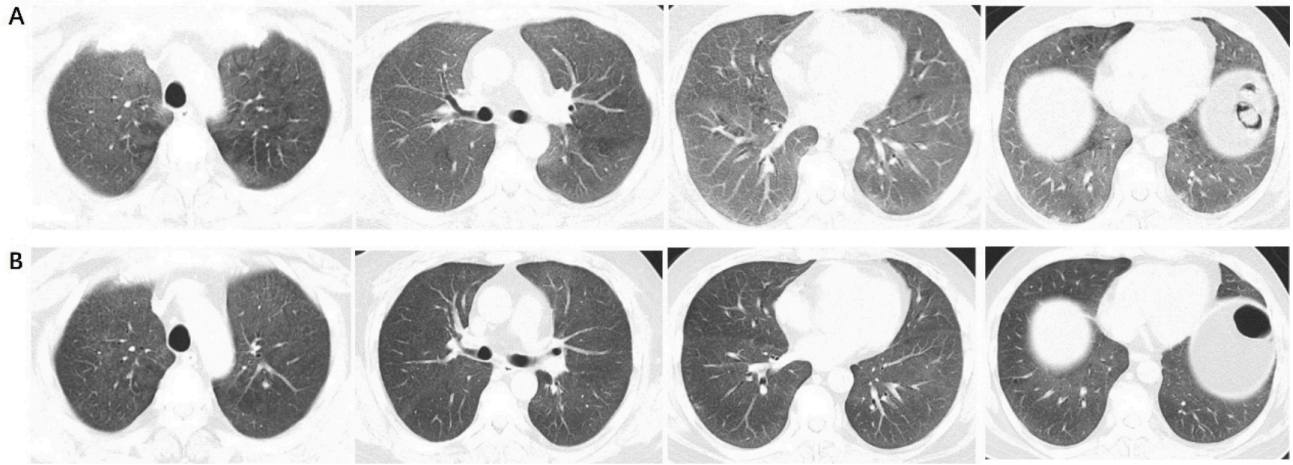


Figure 1

Serial chest computed tomography (CT) findings during the disease course.
(A) Initial CT before diagnosis demonstrating diffuse bilateral ground-glass opacities with mosaic attenuation.
(B) Follow-up CT after sequential bilateral whole-lung lavage demonstrating further radiological improvement.



Figure 2

Bronchoscopic findings and whole-lung lavage.
(A) Characteristic milky bronchoalveolar lavage fluid with abundant proteinaceous sediment, suggestive of pulmonary alveolar proteinosis.

(B) Opaque lavage effluent recovered during sequential whole-lung lavage.

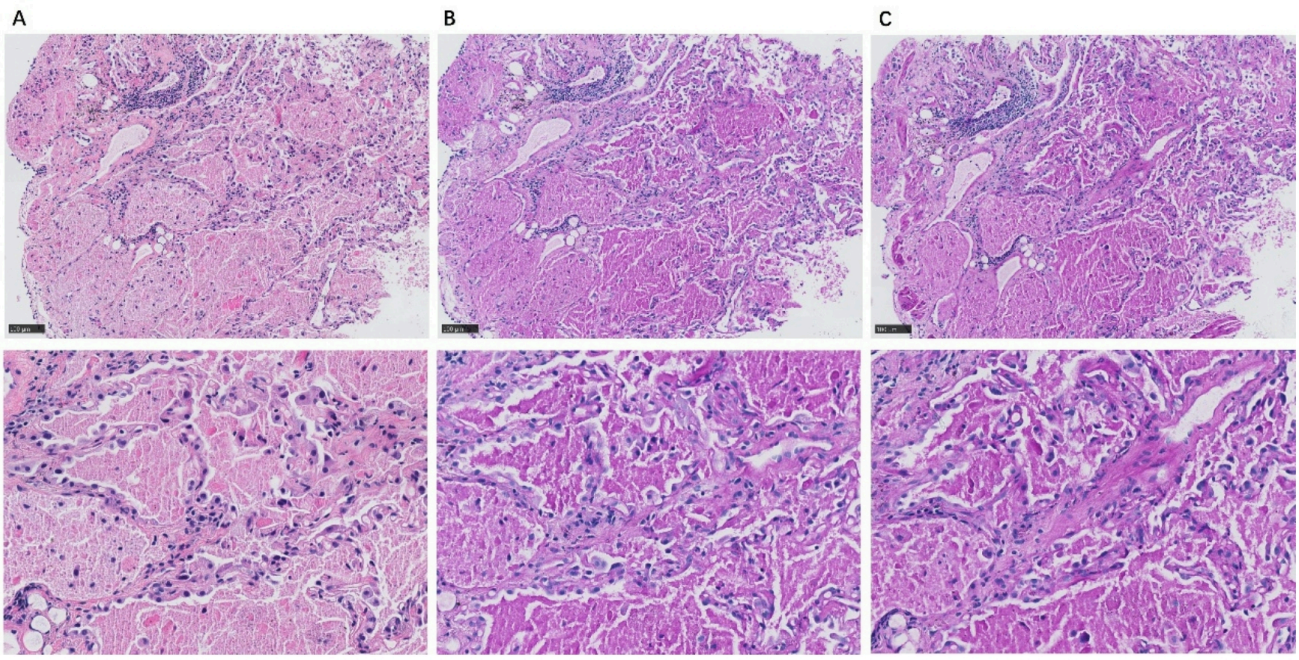


Figure 3

Histopathological findings of transbronchial lung biopsy specimens at ×20 magnification and ×50 magnification
(A) Hematoxylin and eosin staining demonstrating preserved alveolar architecture with intra-alveolar eosinophilic proteinaceous material. (B) Periodic acid–Schiff (PAS) staining showing abundant intra-alveolar PAS-positive material. (C) Diastase-resistant PAS (D-PAS) staining confirming surfactant accumulation.

Supplementary Files

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