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CASE REPORT

Pulmonary alveolar proteinosis: presentation, diagnostic challenges, and management

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Abstract

Pulmonary alveolar proteinosis is a rare diffuse lung disease; diagnosis and treatment of which is often delayed. We present the case study of a 43-year-old male with a six-month history of worsening breathlessness and non-productive cough referred for specialist respiratory input. Rapid investigations, including high-resolution computed tomography (HRCT) and bronchoalveolar lavage, confirmed the diagnosis of pulmonary alveolar proteinosis. Treatment with whole lung lavage significantly improved pulmonary function and quality of life. We discuss the diagnosis and management of this condition and highlight the importance of early recognition and multidisciplinary teamwork in managing pulmonary alveolar proteinosis.

Key words: Interstitial lung disease; Pulmonary alveolar proteinosis; Whole lung lavage

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterised by the accumulation of lipo-proteinaceous surfactant in the alveolar spaces, resulting in impaired gas exchange and type 1 respiratory failure (Salvaterra and Campo, 2020). The non-specific phenotype and rarity of PAP mean that diagnostic delays are common, often leading to significant morbidity and increased healthcare use (McCarthy et al, 2018; Mathavan et al, 2024). 'Segmental endobronchial flooding' to physically remove excess alveolar material was first described in 1963, the procedure of whole lung lavage (WLL) has since been refined, and remains the gold standard treatment (Jouneau et al, 2020). Patients may require repeated procedures but this treatment does not stop surfactant re-accumulation (Campo et al, 2024). In recent years, there has been growing interest in more definitive treatments, particularly with recombinant granulocyte macrophage colony-stimulating factor (GM-CSF) which has increasing data from clinical trials offering new hope for more effective management of PAP (Bonella et al, 2024).

In the following case report, we describe a classical presentation of PAP, detailing the journey from initial presentation through to diagnosis and treatment with WLL, and highlighting why early recognition is crucial for optimal patient outcome.

Case report

Clinical presentation

A 43-year-old male was referred by his general practitioner to the respiratory clinic with a six-month history of worsening breathlessness and a non-productive cough. He denied hemoptysis, changes in appetite or weight. Medical history included asthma diagnosed at age ten, with infrequent use of inhaled therapy. He worked as a domestic builder and ground worker, wearing respiratory protection in high-dust environments. He was a non-smoker with no recent travel history.

On examination, there was no clubbing nor stigmata of respiratory disease. Respiratory rate was elevated at 28 breaths per minute, and chest auscultation was normal. Baseline oxygen saturation was 96%, dropping to 83% after walking 200 metres.

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Investigations

Urgent investigations in the clinic included full blood count (FBC), biochemical profile, C-reactive protein (CRP), immunoglobulins, serum angiotensin-converting enzyme (ACE) levels, human immunodeficiency virus (HIV) serology and an autoimmune screen, all of which showed no abnormalities.

Radiology and pulmonary function tests

Chest X-ray (CXR) demonstrated a diffuse increase in interstitial markings in both lung fields with relative sparing of the apices and costophrenic angles (Figure 1).

High-resolution computed tomography (HRCT) demonstrated widespread ground glass opacification with smooth thickening of the interlobular septa and the intralobular interstitium, producing a 'crazy paving' appearance (Figure 2).

Pulmonary function tests (PFTs) demonstrated preserved spirometry and lung volumes but a reduction in diffusing capacity for carbon monoxide (percent predicted diffusing capacity of the lung for carbon monoxide (DLCO) 63%).

Bronchoscopy

Bronchoscopy and bronchoalveolar lavage (BAL) were performed. At bronchoscopy, airways appeared macroscopically normal and cultures from washings were negative. Bronchoalveolar lavage differential cell count revealed 54% macrophages, 20% epithelial cells, 15% lymphocytes, 10% neutrophils and 0.5% eosinophils. Bronchoalveolar lavage fluid examination demonstrated dense proteinaceous aggregates positive for Periodic Acid-Schiff (PAS) diastase and transbronchial biopsy (TBB) identified dense eosinophilic intra-alveolar material also positive for PAS diastase (Figure 3). These findings were consistent with a diagnosis of PAP.

Diagnosis, initial management, and progress

Diagnosis of PAP was confirmed based on symptoms, and radiological and bronchoscopic findings and discussed at a regional multidisciplinary respiratory meeting. Immunoglobulin G (IgG) antibodies to granulocyte macrophage colony-stimulating factor (GM-CSF) were sent to the national testing laboratory and subsequently were positive confirming autoimmune PAP. The patient underwent WLL three months after his initial presentation at the specialist

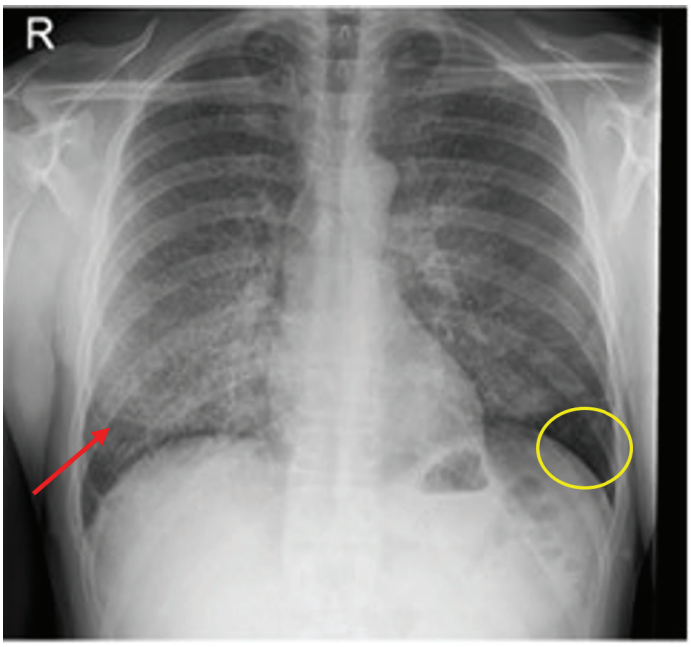

Figure 1. Chest X-ray at presentation. Increased interstitial marking (red arrows) with sparing of costophrenic angles (yellow circle).

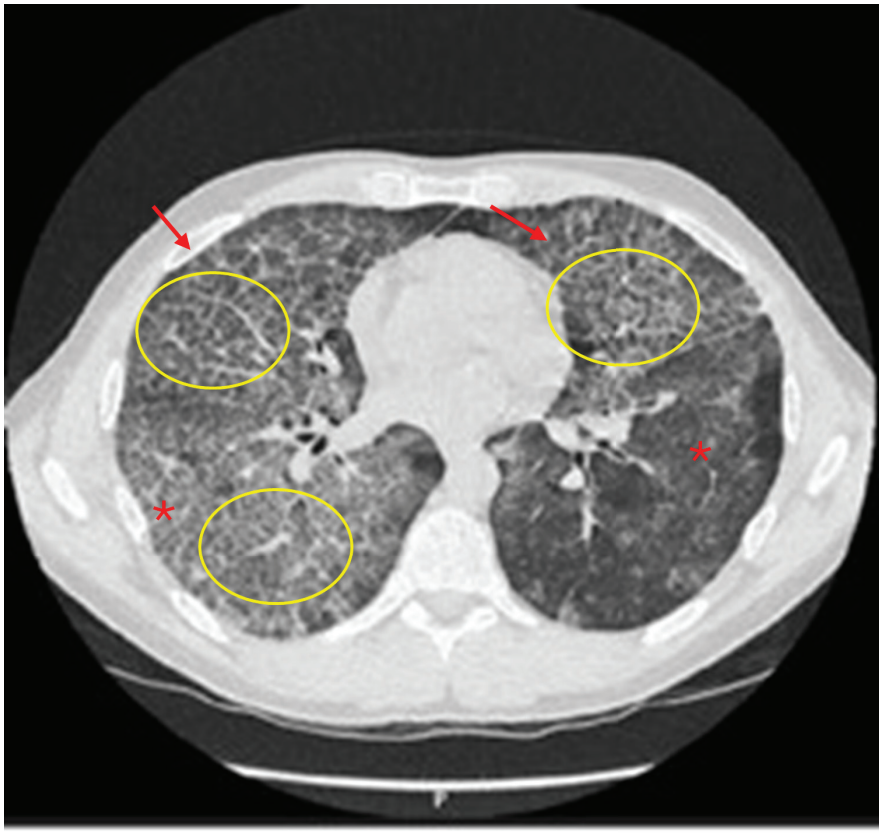

Figure 2. High-resolution computed tomography (HRCT) at presentation. Note interlobular septal thickening (red arrows), diffuse ground-glass opacities (asterisks *) and crazy paving pattern (yellow circle).

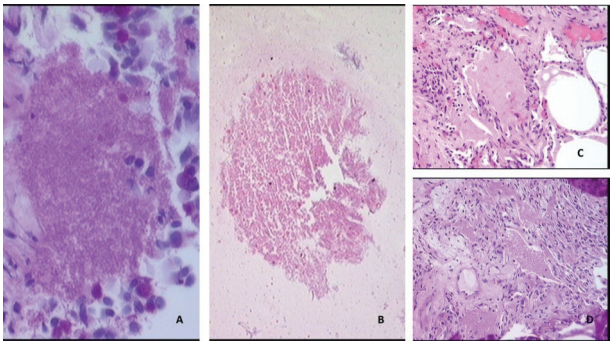

Figure 3. Pathological findings. A,B: Bronchoalveolar lavage fluid. C,D: Transbronchial biopsy images. A. Dense proteinaceous aggregates in bronchoalveolar lavage fluid (20× magnification, Papanicolaou stain). B. Bronchoalveolar lavage fluid aggregates positive for Periodic Acid-Schiff diastase (20× magnification, Periodic Acid-Schiff stain with diastase digestion). C. Dense eosinophilic intra-alveolar material on transbronchial biopsy (20× magnification, Haematoxylin and Eosin Stain). D. Transbronchial biopsy intra-alveolar material positive for Periodic Acid-Schiff diastase (10× magnification, Periodic Acid-Schiff stain with diastase digestion).

centre, with 40 L fluid lavaged from each lung. He reported significant early symptomatic improvement including improved exercise tolerance with less desaturation on objective testing. Post-lavage CXR demonstrated an overall reduction in interstitial markings (Figure 4). The patient has subsequently undergone two additional WLL procedures at four and seven months post-initial WLL. Recent PFTs, post-WLL reveal improved gas transfer with a percent predicted DLCO of 74%. The patient is now being considered for a therapeutic trial of inhaled recombinant GM-CSF via the IMPALA 2 clinical trial (Clinical Trial of

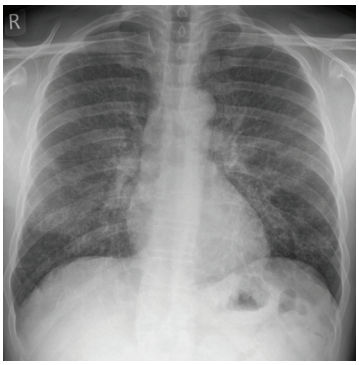

Figure 4. Chest X-ray after 1st whole lung lavage.

Inhaled Molgramostim Nebulizer Solution in Autoimmune Pulmonary Alveolar Proteinosis, NCT04544293).

Discussion

Pulmonary alveolar proteinosis typically affects those aged 40–50 years, with a male-to-female ratio of 2:1 and has an estimated prevalence of seven cases per million (Salvaterra and Campo, 2020). Pulmonary alveolar proteinosis is classified into three forms based on the underlying pathophysiological mechanism: primary, secondary, and congenital (Carrington and Hershberger, 2023). Primary PAP disrupts GM-CSF pathways disrupting surfactant clearance (Jouneau et al, 2020). 90% of primary cases are autoimmune in nature, characterised by the presence of highly specific and sensitive immunoglobulin G GM-CSF antibodies (IgG GM-CSF) (Trapnell et al, 2019; Mathavan et al, 2024). Secondary PAP arises from impaired macrophages associated with various triggers including dust inhalation, haematological cancers, and immunosuppression (Jouneau et al, 2020), while congenital PAP is caused by disorders of surfactant production (Jouneau et al, 2020). Dust inhalation is a recognized risk factor for secondary PAP, however, many patients with primary PAP are also dust-exposed and studies indicate an association between exposure history and autoimmune PAP cases, as demonstrated in this patient (Seymour and Presneill, 2002; Jouneau et al, 2020).

Diagnosis relies on computed tomography (CT) imaging and BAL in a patient presenting with non-specific progressive respiratory symptoms (Jouneau et al, 2020; Salvaterra and Campo, 2020). The ‘crazy paving’ pattern suggests PAP but isn’t pathognomonic, prompting further evaluation with BAL. Bronchoalveolar lavage fluid is typically milky, lymphocyte-predominant and rich in PAS-positive eosinophilic lipoprotein (Carrington and Hershberger, 2023; Jouneau et al, 2020). Lung biopsy demonstrates PAS-positive lipoproteinaceous material but is not essential for diagnosis (Carrington and Hershberger, 2023; Mathavan et al, 2024). Pulmonary function tests typically show a restrictive deficit with significantly impaired DLCO, though normal spirometry can also occur (Jouneau et al, 2020; Salvaterra and Campo, 2020). IgG GM-CSF is the sole clinically relevant biomarker to date (Carrington and Hershberger, 2023).

The clinical course of primary PAP varies from stable to progressive disease with some reports of spontaneous improvement. Common complications include opportunistic infections at intra-and extra-pulmonary sites, with pulmonary fibrosis occurring more rarely (McCarthy et al, 2022). Whole lung lavage is the standard treatment for PAP, but protocols lack standardisation and haven’t been verified in randomised controlled trials. Symptomatic and mortality benefits of this procedure have, however, been observed and reported (Campo et al, 2024; Carrington and Hershberger, 2023). Patients with primary PAP often require repeated WLL, with a reported median time between procedures of 15 months (Campo et al, 2024). Current research using inhaled GM-CSF (iGM-CSF) shows promise as a treatment for autoimmune PAP, with positive results reported. However, optimal dosing, administration protocol, and its role alongside WLL need to be established (Bonella et al, 2024; Campo et al, 2024).

Conclusion

This case highlights the clinical presentation, the importance of appropriate investigations and the multidisciplinary approach needed to manage patients with PAP. The patient had a good response to WLL treatment, but this is only performed in specialised settings and may need to be repeated multiple times. Early recognition and referral to specialist respiratory centres are essential for effective PAP management. Further research is still needed to establish the optimal treatment protocol.

Learning points

- Early recognition of PAP and multidisciplinary involvement are vital for timely and effective management.
- IgG GM-CSF helps to distinguish primary from secondary PAP, particularly in dust-exposed individuals.
- Whole lung lavage is the current standard treatment, but further research is needed to establish the optimal treatment protocol and role of new therapies.
- Post WLL, regular monitoring of symptoms, PFTs and chest imaging is crucial and may indicate the need for additional lavage procedures.

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Availability of data and materials

All the data of this study are included in this article.

Author contributions

RBT diagnosed and was the principal clinician for the patient. MG reviewed patient radiology. AM reviewed pathology. PRO advised on interstitial lung disease management. RBT, JMJ, MG, AM, and PRO were involved in acquisition, analysis, and interpretation of data for the work. JMJ drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

The patient was fully aware of the publication and gave written informed consent as per ethical principles outlined in the Declaration of Helsinki.

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Conflict of interest

The authors declare no conflict of interest.

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