Annals of Clinical Case Reports

Case Report
Published: 15 Jan, 2024

Autoimmune Pulmonary Alveolar Proteinosis Mimicking Connective Tissue Disease-Associated Interstitial Lung Disease: Case Presentation and Mini Literature Review

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Abstract

Pulmonary Alveolar Proteinosis (PAP) is a rare syndrome characterized by alveolar surfactant accumulation and macrophage dysfunction. Differentiating PAP from Connective Tissue Disease-related Interstitial Lung Disease (CTD-ILD) is crucial due to distinct treatment approaches and outcomes. ILD commonly complicates CTDs, but the specific ILD subtypes and their prevalence vary across different conditions. We present the case of a Taiwanese female initially diagnosed with CTD-ILD, later confirmed to have PAP through extensive evaluations. This case underscores the diagnostic challenge of distinguishing PAP from CTD-ILD, emphasizing the critical need to consider PAP in the differential diagnosis, given overlapping features. Timely and precise identification is essential for optimal management and outcomes, as the patient's remarkable improvement following whole lung lavage and Rituximab infusion demonstrates.

Keywords: Pulmonary alveolar proteinosis; Connective tissue disease-related interstitial lung disease; Anti-GM-CSF antibody

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Received Date: *26 Dec 2023*
Accepted Date: *10 Jan 2024*
Published Date: *15 Jan 2024*

Citation:
Tsai WH, Hsieh SC, Li KJ. Autoimmune Pulmonary Alveolar Proteinosis Mimicking Connective Tissue Disease-Associated Interstitial Lung Disease: Case Presentation and Mini Literature Review. Ann Clin Case Rep. 2024; 9: 2558.

ISSN: 2474-1655.

Introduction

Pulmonary Alveolar Proteinosis (PAP) is a rare respiratory syndrome caused by abnormal surfactant buildup in the lungs. PAP has primary, secondary, and congenital forms, each with different causes [1]. Primary PAP is mainly due to GM-CSF signaling issues, with the autoimmune variant being the most common (90%) and driven by anti-GM-CSF autoantibodies [2]. Hereditary PAP results from GM-CSF receptor gene mutations. Secondary PAP is associated with diseases that affect alveolar macrophages, while congenital PAP is linked to surfactant production anomalies [3].

PAP shows varying clinical symptoms, from a slow onset to acute or progressive respiratory failure. Diagnosis involves clinical, radiological, and lab assessments, including anti-GM-CSF autoantibody testing and genetic evaluations [4]. High-resolution chest CT scans play a key role in diagnosing PAP, often revealing characteristic features like "crazy paving" [5]. However, these patterns can make it challenging to distinguish PAP from Interstitial Lung Disease (ILD).

ILD is a common complication in Connective Tissue Diseases (CTDs), significantly impacting patient health. ILD varies across CTDs in terms of prevalence and specific subtype patterns [6]. Detecting subclinical lung abnormalities early is essential for stabilizing CT changes and is best done using high-resolution CT scans. This approach aids in disease management and assessment of lung parenchyma.

Case Presentation

A 56-year-old woman with a history of breast cancer in complete remission following surgery and radiotherapy. She was also initially diagnosed with suspected sicca syndrome. An abnormal chest X-ray result from a health examination conducted five years ago, although she reported no specific symptoms at the time. Subsequent evaluations at Hospital A revealed normal pulmonary function tests but raised suspicion of interstitial lung disease due to patchy ground glass opacities, reticulation, and bronchiectasis seen on chest computed tomography (Figure 1). Despite these findings, the absence of noticeable symptoms led to a lapse in follow-up care.

Seven months prior to her admission to our hospital, the patient experienced progressive dyspnea, severe cough with whitish sputum, and dyspnea at rest. The patient sought medical

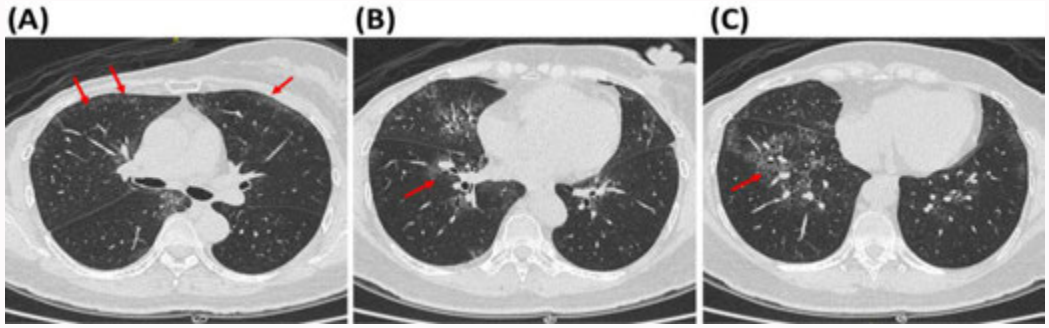

Figure 1: Findings on computed tomography: (A) Subpleural Ground Glass Opacities (GGOs) in bilateral lungs (B, C) Peribronchovascular GGOs in bilateral lungs.

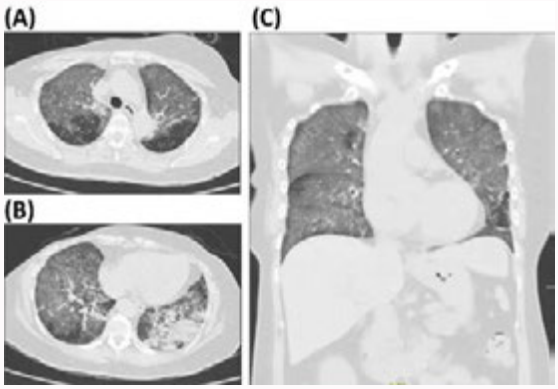

Figure 2: Findings on computed tomography: Progressive and diffuse ground glass opacities (crazy paving pattern) in bilateral lungs with reticulation (A, B) Transverse view (C) Sagittal view.

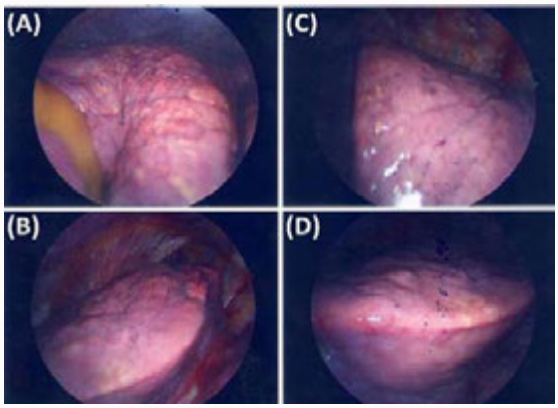

Figure 3: Multiple yellowish irregular surface lesions (Thoracoscopic vision).

attention at Hospital B, where high-resolution CT scans revealed a worsening of bilateral ground glass opacities and reticulation (Figure 2) when compared to prior imaging. The patient was referred to our hospital with a suspected connective tissue disease-related interstitial lung disease. Due to dyspnea and mild desaturation under the nasal cannula, bronchoscopy was not performed. Autoimmune profile testing revealed non-specific results.

To address her worsening condition, the patient underwent a non-intubated uniportal Video-Assisted Thoracoscopic Surgery (VATS) for a left upper lobe wedge resection. During the procedure, multiple yellowish irregular surface lesions were observed in both lungs, along with relatively firm lung parenchymal tissue (Figure 3).

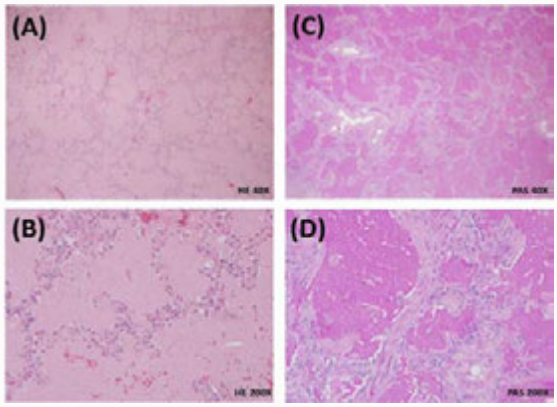

Figure 4: Findings on microscopic view, (A) 40X (B) 200X in HE stain, it shows amorphous, eosinophilic material filling alveolar spaces along with focal interstitial lymphocytic infiltration and foamy cells. (C) 40X (D) 200X in periodic acid-Schiff stain, the eosinophilic material is positive result.

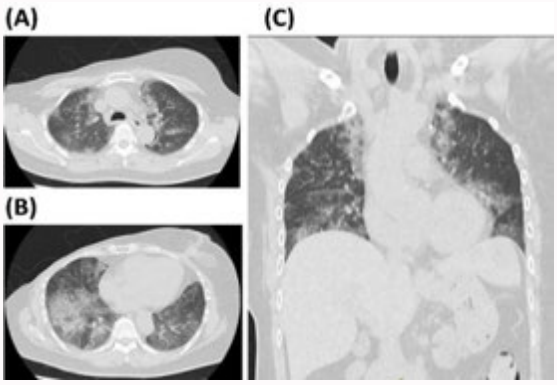

Figure 5: Findings on computed tomography: Diffuse ground glass opacities, improved after treatments compared to previous image studies (A, B) Transverse view (C) Sagittal view.

The frozen biopsy indicated amorphous eosinophilic material filling alveolar spaces with mild lymphocytic infiltrate. Histochemically, the eosinophilic material is positive for periodic acid-Schiff stain (Figure 4), consistent with a diagnosis of Pulmonary Alveolar Proteinosis (PAP). Furthermore, an elevated Anti-GM CSF antibody titer was noted.

Treatment with high-flow nasal cannula improved the patient's condition gradually due to a low P/F ratio, precluding whole lung lavage. Rituximab was prescribed, leading to progressive improvement. Subsequent chest CT scans showed resolution of PAP

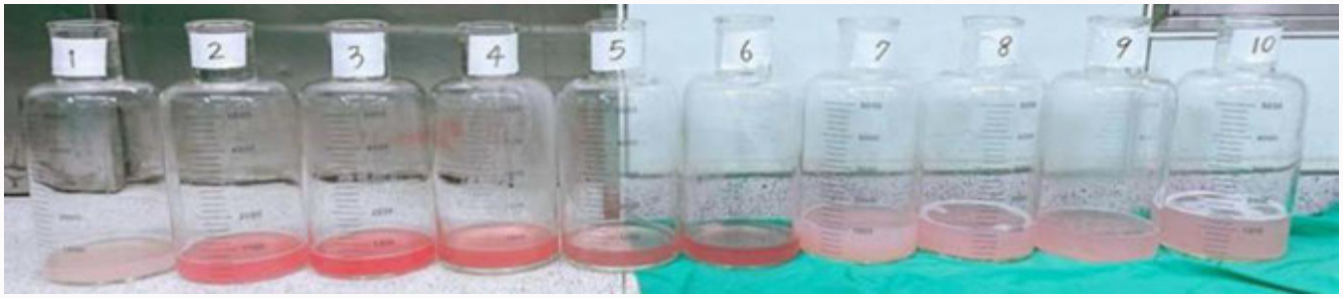

Figure 6: Whole lung lavage: Texture ranging from orange to a milky consistency.

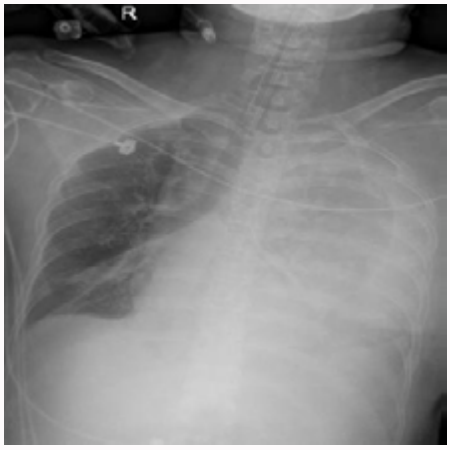

Figure 7: Post-lung lavage left lung white out, revealed left lung pleural effusion.

(Figure 5). For further disease control, the patient was admitted for a whole lung lavage to alleviate her symptoms. The right lung lavage was performed successfully, resulting in relief for the patient. The lavage fluid exhibited a texture ranging from orange to a milky consistency (Figure 6), and the patient tolerated the procedure well. However, following the left whole lung lavage, a chest X-ray revealed a white-out of the left lung (Figure 7). Subsequent imaging showed left pleural effusion, which was managed with thoracocentesis, draining 840cc of transparent-pinkish pleural effusion. In stable condition, the patient was discharged with an outpatient clinic follow-up appointment, with no reported severe adverse drug reactions during follow-up care.

Discussion

Pulmonary Alveolar Proteinosis (PAP) remains a complex and rare pulmonary disorder, characterized by the accumulation of surfactant lipoproteins within the alveoli. This condition can manifest in various forms, including primary, secondary, and congenital PAP, each with distinct etiological mechanisms [1]. Our case underscores the significance of timely and accurate diagnosis in the context of PAP, especially given the potential for overlapping clinical and radiological features with other respiratory conditions, including Interstitial Lung Disease (ILD).

The classification of PAP into primary and secondary forms has been a cornerstone in understanding this condition. In particular, primary PAP is frequently associated with autoimmune PAP, which constitutes the majority of cases. The presence of anti-GM-CSF autoantibodies is a key feature in autoimmune PAP, indicating an aberration in GM-CSF signaling [4]. In addition, the advent of targeted therapies, such as rituximab, has provided a new approach to the treatment of autoimmune PAP [7]. Rituximab, a monoclonal antibody that targets B cells, has shown promising results in ameliorating the production of anti-GM-CSF autoantibodies and improving clinical outcomes. In our case, rituximab played a pivotal role in the patient's treatment, underscoring the significance of personalized therapeutic strategies in PAP management [8].

Furthermore, the challenges associated with the differential diagnosis between PAP and ILD, as observed in our case, emphasize the need for comprehensive assessments, including radiological and clinical evaluations, to distinguish between these conditions. The role of High-Resolution chest Computed Tomography (HRCT) in the diagnosis of PAP is well-established [5]. While "crazy paving" patterns are often seen in PAP, distinguishing these radiological features from ILD can be challenging.

Additionally, our case serves as a reminder of the significant impact of ILD in CTDs and the diverse spectrum of ILD subtypes associated with different CTDs. Advances in understanding the pathogenesis of CTD-ILDs, including the roles of cytokines and autoantibodies, have fueled the exploration of targeted therapies in these conditions [9].

Our case highlights the evolving landscape of PAP diagnosis and management, particularly in the context of autoimmune PAP. It emphasizes the critical role of targeted therapies, such as rituximab, in improving patient outcomes. Furthermore, the challenges in distinguishing PAP from ILD highlight the need for continued research in refining diagnostic approaches. The broader perspective on CTD-ILDs underscores the need for a multidisciplinary approach to the management of these complex conditions [10].

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