Pulmonary alveolar proteinosis: It's not surfactant overproduction

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Autoimmune pulmonary alveolar proteinosis (aPAP) presents a distinct challenge in respiratory medicine, characterised by the accumulation of lipoproteinaceous material within the alveoli. This rare condition, often misdiagnosed, stems from a specific immunological dysfunction rather than infection or environmental exposure. Understanding its precise mechanisms is essential for effective clinical management, which has historically relied on invasive procedures.

KEY TAKEAWAYS

- The Pivot: aPAP is driven by neutralising autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF), disrupting alveolar macrophage function.
- The Data: Whole lung lavage remains the cornerstone of treatment, but its invasiveness and the need for repeated procedures highlight an unmet need for less burdensome therapies.
- The Action: Clinicians should consider aPAP in patients presenting with unexplained progressive dyspnoea and diffuse alveolar opacities, pursuing GM-CSF autoantibody testing early in the diagnostic pathway.

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disorder defined by the excessive accumulation of surfactant phospholipids and proteins within the alveolar spaces. This build-up impairs gas exchange, leading to progressive dyspnoea, cough, and often, hypoxemia. The underlying pathology is not a defect in surfactant production, but rather a failure of alveolar macrophages to clear surfactant effectively. This failure is directly attributable to neutralising autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF).
GM-CSF is a vital cytokine for the differentiation, maturation, and function of alveolar macrophages, impacting the ability to maintain lung function. These macrophages are the primary cells responsible for maintaining alveolar homeostasis by phagocytosing excess surfactant. When autoantibodies bind to GM-CSF, they effectively block its interaction with its receptor on alveolar macrophages, rendering these cells dysfunctional. The consequence is a progressive accumulation of surfactant material, which can eventually fill the alveoli, leading to significant respiratory compromise. This mechanism distinguishes aPAP from other forms of pulmonary alveolar proteinosis, such as secondary PAP (associated with haematologic malignancies, immunodeficiency, or environmental exposures) and congenital PAP (due to genetic mutations affecting surfactant metabolism).

The Pathophysiological Basis of aPAP

The core defect in aPAP lies in the disruption of the GM-CSF signaling pathway. GM-CSF is produced by various cell types in the lung, including alveolar epithelial cells, and acts locally to support alveolar macrophage viability

and function. Specifically, it promotes the expression of genes involved in surfactant catabolism and phagocytosis. The autoantibodies found in aPAP patients are predominantly IgG antibodies that bind to GM-CSF with high affinity, preventing it from activating its receptor. This blockade leads to a severe functional deficiency of alveolar macrophages, even in the presence of normal or elevated levels of GM-CSF protein.

The impaired macrophage function results in a characteristic histological pattern: alveoli filled with eosinophilic, granular material that stains positive for periodic acid-Schiff (PAS) and contains cholesterol clefts. The alveolar septa typically remain intact, differentiating aPAP from other interstitial lung diseases. The disease often presents insidiously, with symptoms like progressive dyspnoea on exertion, fatigue, and a non-productive cough. Some patients may experience recurrent pulmonary infections due to impaired host defence mechanisms, as dysfunctional macrophages also compromise the clearance of pathogens. The diagnosis is often delayed due to the non-specific nature of early symptoms and the rarity of the condition, requiring a high index of suspicion from clinicians. For a broader understanding of interstitial lung diseases, clinicians might consult resources like the ILD Diagnosis and Management: A Practical ATS 2026 Update.

Diagnostic Approaches and Clinical Presentation

Diagnosing aPAP involves a combination of clinical suspicion, imaging, and specific laboratory tests. High-resolution computed tomography (HRCT) of the chest typically reveals a characteristic 'crazy-paving' pattern, consisting of ground-glass opacities superimposed on interlobular septal thickening. This pattern, while highly suggestive, is not pathognomonic and can be seen in other conditions, including acute respiratory distress syndrome (ARDS) and certain infections. Therefore, further investigation is essential.

Bronchoalveolar lavage (BAL) is a key diagnostic tool. The BAL fluid in aPAP patients is typically milky or turbid due to the high lipid content, and microscopic examination reveals abundant PAS-positive lipoproteinaceous material within alveolar macrophages and extracellularly. The definitive diagnosis of aPAP relies on the detection of high titres of anti-GM-CSF autoantibodies in serum, which is essential for accurate patient classification. This serological test has high sensitivity and specificity, making it the gold standard for confirming aPAP and differentiating it from other forms of PAP. Lung biopsy, while historically used, is now often reserved for cases where the diagnosis remains unclear after serological testing and BAL, given its invasive nature. The Oxford Handbook of Respiratory Medicine provides a concise reference for such diagnostic pathways.

Current Management Strategies

The primary treatment for aPAP remains whole lung lavage (WLL), a procedure that mechanically removes the accumulated surfactant from the alveoli. WLL involves sequentially lavaging one lung while the other is ventilated, typically under general anaesthesia. This procedure can significantly improve gas exchange and reduce symptoms, but its effects are often temporary, requiring repeated lavages over time. The frequency of WLL depends on disease severity and recurrence, with some patients needing procedures every few months to maintain lung function. The invasiveness of WLL, coupled with the need for repeated hospitalisations, places a significant burden on patients and healthcare systems.

Beyond WLL, other therapeutic approaches have been explored, though none have achieved the same level of efficacy as WLL for acute symptom relief. Recombinant human GM-CSF (rhGM-CSF) therapy aims to overcome the neutralising

effects of autoantibodies by providing exogenous GM-CSF. This approach has shown variable success, with some patients experiencing clinical and radiological improvement, while others do not respond. The efficacy of rhGM-CSF may depend on the titre and affinity of the autoantibodies, as well as the route and dose of administration (subcutaneous versus inhaled). Inhaled rhGM-CSF is generally better tolerated than subcutaneous administration, which can be associated with systemic side effects.

Immunosuppressive therapies, such as corticosteroids, have generally not shown consistent benefit in aPAP and are not recommended as a primary treatment. This is because the disease is driven by autoantibodies, not by a generalised inflammatory process that would typically respond to immunosuppression. Rituximab, a B-cell depleting antibody, has been used in some refractory cases, targeting the B cells responsible for producing the anti-GM-CSF autoantibodies. While case reports and small series suggest potential benefit, larger controlled studies are needed to establish its role and optimal dosing in aPAP. The management of autoimmune conditions affecting the lung often benefits from a multidisciplinary approach, integrating pulmonology with rheumatology and immunology expertise.

Unmet Needs and Future Directions

Despite the established efficacy of WLL, the chronic, relapsing nature of aPAP and the invasiveness of the procedure highlight a substantial unmet need for more convenient and targeted therapies. The variability in response to rhGM-CSF also points to the need for better patient stratification and novel agents. Research efforts are focused on developing therapies that more effectively neutralise or eliminate the anti-GM-CSF autoantibodies, or that bypass the GM-CSF pathway altogether to restore alveolar macrophage function.

One area of investigation involves plasmapheresis or immunoadsorption to remove circulating autoantibodies, which could offer temporary relief but would likely require repeated treatments. Another avenue that shows potential is the development of small molecules that can modulate GM-CSF receptor signaling downstream of the autoantibody blockade, or agents that promote surfactant clearance through alternative pathways. Gene therapy approaches to deliver functional GM-CSF to the lung are also being explored, though these are still in early stages of development. The goal is to move beyond symptomatic management with WLL towards disease-modifying therapies that can offer sustained remission and improve quality of life for patients with aPAP. Understanding the intricate mechanisms of diseases like sarcoidosis also informs our approach to other complex pulmonary conditions, as discussed in Sarcoidosis: Current Understanding of Diagnosis and Management.

> **CLINICAL IMPLICATIONS**
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> The persistent reliance on whole lung lavage for autoimmune pulmonary alveolar proteinosis is a stark reminder of the limitations in treating rare, complex immunological diseases. While effective, WLL is a brute-force solution, demanding significant resources and imposing a heavy burden on patients who face repeated procedures.
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> The variable response to recombinant GM-CSF highlights the heterogeneity of the disease and the need for better biomarkers to predict treatment success. Simply providing more GM-CSF does not always overcome the autoantibody blockade, suggesting that the quality and quantity of these antibodies matter. We need to understand why some patients respond and others do not, rather than treating all cases as uniform.
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> For clinicians, the key takeaway is early and accurate diagnosis, leveraging GM-CSF autoantibody testing to

> differentiate aPAP from other interstitial lung diseases. This precision avoids unnecessary biopsies and guides appropriate management. The development of less invasive, targeted therapies remains the critical next step for improving patient outcomes and reducing the long-term impact of this debilitating condition.

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