

Dyspnea and Deception: Overcoming Diagnostic Hurdles in Pulmonary Alveolar Proteinosis

Ketan Jolly ¹, Merry Mathew ¹, Hanieh Tabatabaei ¹, Barath Rangaswamy ¹

¹. Department of Internal Medicine, Texas Tech University Health Sciences Center, Odessa, USA

Corresponding author: Ketan Jolly, ketanjolly@gmail.com

Review began 05/05/2025

Review ended 05/19/2025

Published 05/21/2025

© Copyright 2025

Jolly et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.84562

Abstract

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disorder characterized by abnormal surfactant accumulation due to defective alveolar macrophage clearance. It often presents with exertional dyspnea and nonspecific imaging findings, commonly leading to diagnostic delays. We present the case of a 56-year-old woman with progressive hypoxia initially misattributed to acute respiratory distress syndrome, noncardiogenic pulmonary edema, and hypersensitivity pneumonitis. Corticosteroids were initiated based on early differential considerations. Further evaluation revealed concurrent methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and bronchoalveolar lavage findings suggestive of PAP. Following stabilization and treatment of the infection, transbronchial biopsy confirmed PAP. The patient required prolonged intensive care and was ultimately transferred for whole-lung lavage. This case highlights the critical importance of early recognition of PAP in patients with characteristic imaging findings and progressive respiratory failure. Misdiagnosis can lead to inappropriate therapies and increased risk of infectious complications.

Categories: Pathology, Allergy/Immunology, Pulmonology

Keywords: autoimmune pulmonary alveolar proteinosis, bronchoalveolar lavage, crazy paving pattern, granulocyte macrophage colony stimulating factor, hypoxemic respiratory failure, methicillin-resistant staphylococcus aureus, secondary pulmonary infection, transbronchial lung biopsy, whole-lung lavage

Introduction

Pulmonary alveolar proteinosis (PAP) is a pulmonary disease characterized by alveolar surfactant accumulation due to defective clearance by alveolar macrophages [1]. It is rare, with a prevalence of around seven cases per million people [2]. Among affected individuals, there is a high prevalence of smokers and exposure to inhaled dust [3,4]. Three primary pathways lead to PAP: autoimmune (90% of cases), secondary, and hereditary. The pathophysiology is linked to granulocyte macrophage colony-stimulating factor (GM-CSF), a cytokine essential for alveolar macrophage function [5,6].

Clinical symptoms are often nonspecific, and 31% of patients are asymptomatic. When symptomatic, exertional dyspnea and cough are the most common manifestations, while fever and weight loss are rare [4]. Chest X-ray typically reveals bilateral opacities with consolidation or air bronchograms in a perihilar and basal distribution. On high-resolution computed tomography (CT) of the chest, a characteristic but nonspecific “crazy paving” pattern is observed, consisting of intra-alveolar ground-glass opacities and interlobular septal thickening [3,7]. Large focal airspace disease, mediastinal adenopathy, and pulmonary nodules are rare and should raise suspicion for underlying malignancy or infection [7].

Bronchoalveolar lavage (BAL) is diagnostic, and most cases can be diagnosed without lung biopsy [1,3]. The lavage fluid is typically milky, and histologic findings include large, foamy alveolar macrophages, eosinophilic bodies and granules, and proteinaceous material with positive periodic acid-Schiff (PAS) staining and negative Alcian blue staining [1]. Autoimmune PAP can be confirmed through the detection of anti-GM-CSF antibodies via enzyme-linked immunosorbent assay [1].

Whole-lung lavage remains the standard treatment, resulting in clinical and radiographic improvement in most cases [1]. For autoimmune PAP, subcutaneous and inhaled GM-CSF therapies offer less invasive treatment approaches that have demonstrated therapeutic efficacy [8–11].

Case Presentation

A 56-year-old woman with a medical history of non-insulin-dependent diabetes mellitus, hypertension, and prior *Nocardia* infection presented to the pulmonology clinic with progressive shortness of breath, first noted two months before admission. She was a lifetime non-smoker. She reported dyspnea on exertion and significant hypoxia during ambulation but denied cough or fever. A chest radiograph by her primary care physician showed abnormalities, leading to a referral to a pulmonologist. A high-resolution chest CT revealed severe diffuse lung disease with ground-glass opacities with a “crazy paving” appearance, though subpleural disease was absent (Figure 1). Differential diagnoses included recurring *Nocardia* infection, acute

How to cite this article

Jolly K, Mathew M, Tabatabaei H, et al. (May 21, 2025) Dyspnea and Deception: Overcoming Diagnostic Hurdles in Pulmonary Alveolar Proteinosis. Cureus 17(5): e84562. DOI 10.7759/cureus.84562

respiratory distress syndrome (ARDS), noncardiogenic pulmonary edema, and hypersensitivity pneumonitis.



FIGURE 1: Computed tomography (CT) of chest showing a characteristic “crazy paving” appearance.

The patient was admitted for further evaluation. On admission, the physical exam revealed poor bilateral air entry with inspiratory crackles; other findings were unremarkable. Laboratory tests showed elevated hemoglobin (17.7 g/dL, normal 12-16 g/dL) and elevated hematocrit (53.7%, normal 36-48%), consistent with polycythemia likely secondary to chronic hypoxia. Arterial blood gas from the clinic showed hypoxemic respiratory failure with a pH of 7.365, partial pressure of oxygen (pO_2) of 50 mmHg, and partial pressure of carbon dioxide (pCO_2) of 29.8 mmHg.

A fiberoptic bronchoscopy with BAL was performed, with white, opaque lavage fluid samples obtained from the right middle lobe and left upper lobe. Due to severe hypoxia, transbronchial biopsies were deferred. Following the procedure, the patient could not be extubated and required transfer to the intensive care unit (ICU) for mechanical ventilation. On day two of hospitalization, the patient was extubated and placed on a high-flow nasal cannula to manage oxygenation. Chest X-rays showed persistent diffuse bilateral infiltrates with no pneumothorax or large pleural effusions (Figure 2). The patient's imaging findings raised suspicion for PAP, given the radiological findings and oxygenation challenges. The patient also tested positive for methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia with respiratory cultures obtained at the time of bronchoscopy. She was started on a 10-day course of linezolid for MRSA coverage. She was also started on trimethoprim-sulfamethoxazole due to concern for recurring *Nocardia* infection. Despite treatment, the patient experienced fluctuating oxygen needs, requiring intermittent non-invasive ventilation.

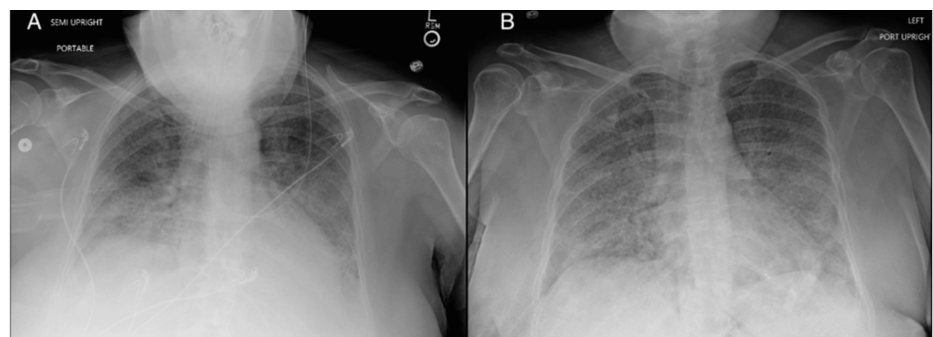


FIGURE 2: Chest X-rays showing severe diffuse lung infiltrates on hospital day 2 (A) and day 21 (B).

Close ICU monitoring and supportive care continued. Thoracic surgery was consulted regarding a lung biopsy, but conservative management with steroids was favored at first due to her instability. Over the following days, the patient's condition improved, and she completed treatment for MRSA pneumonia. At that time, transbronchial biopsies were completed and sent to pathology. Biopsy results demonstrated PAS-positive amorphous, eosinophilic material filling alveolar spaces, confirming the diagnosis of PAP (Figures 3-4). No organisms were seen on silver staining, ruling out nocardiosis. After stabilization, the patient was discharged from the ICU on day 27 of hospitalization. She was transferred to another facility for whole-lung lavage because the necessary equipment was unavailable at this facility.

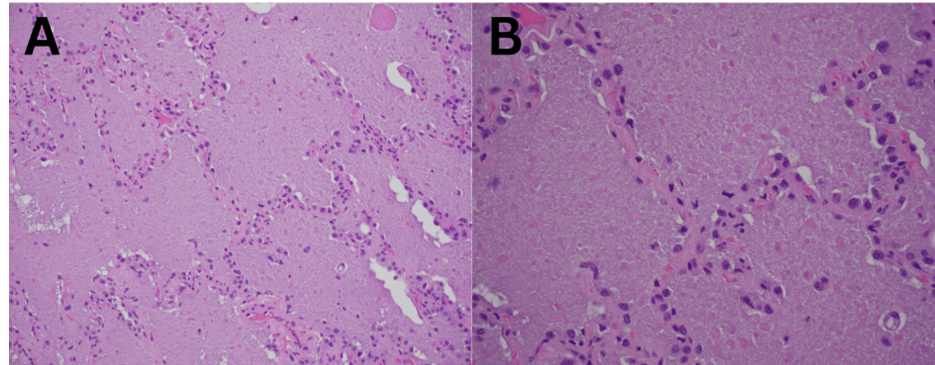


FIGURE 3: Micrograph showing alveoli filled with amorphous, eosinophilic debris containing occasional globules; hematoxylin & eosin (H&E) stain: medium power (A), high power (B).

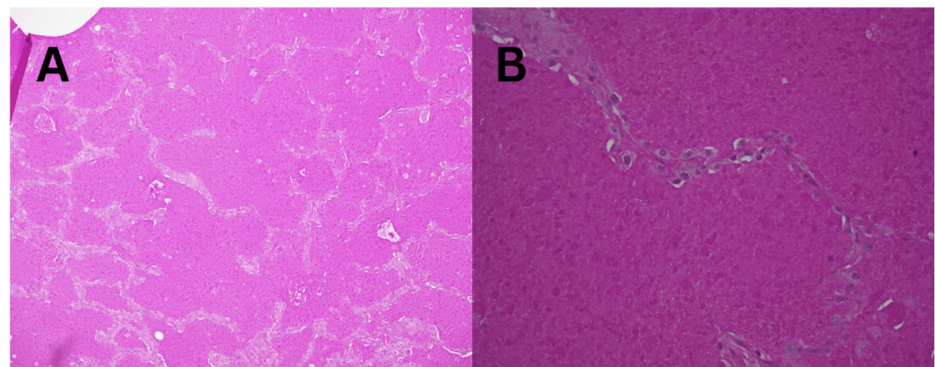


FIGURE 4: Positive periodic acid-Schiff staining of lung tissue; medium power (A), high power (B).

Discussion

PAP is a rare condition marked by alveolar surfactant accumulation in alveoli [1]. A large American study found the prevalence of PAP to be around seven cases per million people, with male and female individuals being affected equally. The prevalence is likely underestimated due to challenges and delays in diagnosis. PAP incidence increases with age, demonstrating a bimodal distribution peaking between ages 45-54 years and again at 65 years and older [2]. Patients with PAP also exhibit a higher burden of comorbidities, greater healthcare utilization, and significantly higher annual healthcare costs compared to matched controls [2].

Exertional dyspnea and cough are the most common symptoms, although approximately one-third of patients are asymptomatic [4]. Typically, PAP follows a progressive and indolent course. This case was distinctive due to the patient's severe hypoxemia, secondary polycythemia, and requirement for mechanical ventilation, an uncommon severity. The exacerbation of symptoms was likely due to a combination of underlying PAP and secondary MRSA pneumonia.

Diagnosing PAP presents significant challenges due to its nonspecific clinical features and overlapping imaging findings. The patient's initial differential diagnosis included ARDS, noncardiogenic pulmonary edema, and hypersensitivity pneumonitis. These conditions can exhibit similar imaging features, such as ground-glass opacities and interlobular septal thickening, commonly referred to as the "crazy paving" pattern [12]. In PAP, this pattern arises from the accumulation of surfactant and PAS-positive proteinaceous

material in the alveoli, leading to impaired gas exchange and respiratory symptoms [13]. The broad differential and diagnostic uncertainty in the current case led to the initiation of corticosteroid therapy, which can worsen autoimmune PAP severity and increase the risk of infections [14].

The patient's prior history of nocardiosis further complicated the diagnostic evaluation. Clinically, nocardiosis typically presents with a cough that may start dry but progresses to purulent sputum or hemoptysis [15]. In PAP, the cough is often initially non-productive but can worsen as surfactant accumulation increases [16]. On imaging, both conditions can show bilateral reticulonodular opacities [12,17], though cavitary lesions are more suggestive of nocardiosis, particularly in immunocompromised individuals [17].

Recent advancements in PAP treatment have introduced novel therapeutic options [8-11]. Inhaled GM-CSF therapy (molgramostim) demonstrated significant improvements in alveolar-arterial oxygen gradients and functional status in patients with autoimmune PAP in a multicenter randomized controlled trial [18]. A subsequent phase three clinical trial confirmed molgramostim's ability to improve lung function and its favorable tolerability profile [19]. Additionally, a plasmapheresis protocol with a measurable decrease of anti-GM-CSF antibodies demonstrated reduced symptoms and improved lung function, resulting in the reduction of whole-lung lavage frequency [20].

Longitudinal data from a Japanese cohort highlight the variability in PAP's natural history [4]. Among those diagnosed within one year, 66% experienced unchanged symptoms. In patients with intermediate disease duration (1-10 years), 42.5% improved, 29.8% worsened, and 27.7% remained unchanged. In individuals with disease exceeding 10 years, nearly two-thirds experienced worsening symptoms. Notably, 28.2% of asymptomatic individuals experienced spontaneous improvement without requiring whole-lung lavage [4].

This case underscores the importance of maintaining a broad differential diagnosis in patients presenting with progressive hypoxemia and characteristic "crazy paving" patterns. Early recognition and management of PAP are critical to optimizing patient outcomes and preventing unnecessary therapeutic interventions.

Conclusions

In this report, we presented a rare, severe manifestation of PAP in a 56-year-old woman, complicated by secondary MRSA pneumonia. Her symptoms of severe hypoxemia, secondary polycythemia, and eventual requirement for mechanical ventilation underscore a rare potential of the disease to escalate in complexity. Challenges in diagnosis led to the initiation of corticosteroid therapy, which can worsen autoimmune PAP disease severity and increase infection risk. This highlights the importance of timely and accurate diagnosis in PAP patients. Inhaled GM-CSF shows promise in providing a less invasive option for autoimmune PAP management and offers a potential treatment alternative in locations where equipment for whole-lung lavage is lacking.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ketan Jolly, Barath Rangaswamy, Merry Mathew, Hanieh Tabatabaei

Acquisition, analysis, or interpretation of data: Ketan Jolly, Merry Mathew

Drafting of the manuscript: Ketan Jolly, Merry Mathew, Hanieh Tabatabaei

Critical review of the manuscript for important intellectual content: Ketan Jolly, Barath Rangaswamy, Merry Mathew, Hanieh Tabatabaei

Supervision: Barath Rangaswamy

Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

Ketan Jolly and Merry Mathew contributed equally to the work and should be considered co-first authors.

References

1. Borie R, Danel C, Debray MP, et al.: Pulmonary alveolar proteinosis. *Eur Respir Rev*. 2011, 20:98-107. [10.1183/09059180.00001311](https://doi.org/10.1183/09059180.00001311)
2. McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC: Prevalence and healthcare burden of pulmonary alveolar proteinosis. *Orphanet J Rare Dis*. 2018, 13:129. [10.1186/s13023-018-0846-y](https://doi.org/10.1186/s13023-018-0846-y)
3. Briens E, Delaval P, Mairesse MP, Valeyre D, Wallaert B, Lazor R, Cordier JF: Pulmonary alveolar proteinosis [Article in French]. *Rev Mal Respir*. 2002, 19:166-182.
4. Inoue Y, Trapnell BC, Tazawa R, et al.: Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med*. 2008, 177:752-62. [10.1164/rccm.200708-1271OC](https://doi.org/10.1164/rccm.200708-1271OC)
5. Dranoff G, Crawford AD, Sadelain M, et al.: Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. *Science*. 1994, 264:713-6. [10.1126/science.8171324](https://doi.org/10.1126/science.8171324)
6. Stanley E, Lieschke GJ, Grail D, et al.: Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. *Proc Natl Acad Sci U S A*. 1994, 91:5592-6. [10.1073/pnas.91.12.5592](https://doi.org/10.1073/pnas.91.12.5592)
7. Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM: CT features of pulmonary alveolar proteinosis. *AJR Am J Roentgenol*. 2001, 176:1287-94. [10.2214/ajr.176.5.1761287](https://doi.org/10.2214/ajr.176.5.1761287)
8. Venkateshiah SB, Yan TD, Bonfield TL, Thomassen MJ, Meziane M, Czich C, Kavuru MS: An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. *Chest*. 2006, 130:227-37. [10.1378/chest.130.1.227](https://doi.org/10.1378/chest.130.1.227)
9. Seymour JF, Presneill JJ, Schoch OD, et al.: Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. *Am J Respir Crit Care Med*. 2001, 163:524-31. [10.1164/ajrccm.163.2.2003146](https://doi.org/10.1164/ajrccm.163.2.2003146)
10. Tazawa R, Trapnell BC, Inoue Y, et al.: Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. *Am J Respir Crit Care Med*. 2010, 181:1345-54. [10.1164/rccm.200906-0978OC](https://doi.org/10.1164/rccm.200906-0978OC)
11. Wylam ME, Ten R, Prakash UB, Nadrous HF, Clawson ML, Anderson PM: Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis. *Eur Respir J*. 2006, 27:585-93. [10.1183/09031936.06.00058305](https://doi.org/10.1183/09031936.06.00058305)
12. Galhenage J, Weerasinghe B, Dilesha W, Constantine R, Gunasena B: Pulmonary alveolar proteinosis and first successful whole lung lavage in Sri Lanka: a case report. *J Med Case Rep*. 2017, 11:62. [10.1186/s13256-017-1218-2](https://doi.org/10.1186/s13256-017-1218-2)
13. Ghavidel A: Pulmonary alveolar proteinosis, unusual infiltrative lung disease, the dilemma for physicians: a case report and literature review. *J Anal Res Clin Med*. 2017, 5:141-5. [10.15171/jarcm.2017.027](https://doi.org/10.15171/jarcm.2017.027)
14. Akasaka K, Tanaka T, Kitamura N, et al.: Outcome of corticosteroid administration in autoimmune pulmonary alveolar proteinosis: a retrospective cohort study. *BMC Pulm Med*. 2015, 15:88. [10.1186/s12890-015-0085-0](https://doi.org/10.1186/s12890-015-0085-0)
15. Mahat JB, Hussien S, Negassa RM, Reddy Y, Ayele GM, Michael MB: Nocardia in an immunocompetent host masquerading as lung cancer: a case report. *Cureus*. 2022, 14:e27039. [10.7759/cureus.27039](https://doi.org/10.7759/cureus.27039)
16. Oda N, Tamai K, Suzuki Y, Yoshimatsu H, Matsuoka H, Matsumoto Y, Okada N: Marked improvement in autoimmune pulmonary alveolar proteinosis with severe hypoxemia in a patient treated with ambroxol: a case report. *J Med Case Rep*. 2015, 9:100. [10.1186/s13256-015-0588-6](https://doi.org/10.1186/s13256-015-0588-6)
17. Shariff M, Gunasekaran J: Pulmonary nocardiosis: review of cases and an update. *Can Respir J*. 2016, 2016:7494202. [10.1155/2016/7494202](https://doi.org/10.1155/2016/7494202)
18. Trapnell BC, Inoue Y, Bonella F, et al.: Inhaled molgramostim therapy in autoimmune pulmonary alveolar proteinosis. *N Engl J Med*. 2020, 383:1635-44. [10.1056/NEJMoa1913590](https://doi.org/10.1056/NEJMoa1913590)
19. Trapnell BC: Inhaled molgramostim therapy for the treatment of autoimmune pulmonary alveolar proteinosis (aPAP): a plain language summary of the IMPALA trial. *Hosp Pract (1995)*. 2024, 52:47-63. [10.1080/21548331.2024.2367955](https://doi.org/10.1080/21548331.2024.2367955)
20. Garber B, Albores J, Wang T, Neville TH: A plasmapheresis protocol for refractory pulmonary alveolar proteinosis. *Lung*. 2015, 193:209-11. [10.1007/s00408-014-9678-2](https://doi.org/10.1007/s00408-014-9678-2)