AMSER Case of the Month September 2025

66-year-old female with malaise and shortness of breath for 3-months

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Patient Presentation

History of Present Illness:

66-year-old woman initially presented to an urgent care center with flu-like symptoms; diagnosed with an asthma exacerbation, and discharged on prednisone

Following completion of prednisone therapy, the malaise and dyspnea returned

Symptoms were mild but have persisted for 3-months

No reported cough, wheezing, chest pain, fever, or chills

Past Medical History: Asthma, seizures

Pertinent Family History:

Father diagnosed with non-small cell lung cancer (NSCLC)

Sister diagnosed with asthma and idiopathic pulmonary fibrosis (IPF)

Social History:

Life-long non-smoker, denies recreational drugs

Lives in a barn with 3 dogs, 1 horse, and a donkey; no birds or chickens

She walks her dogs 2 miles/day

Employed as an Army Certified Registered Nurse Anesthetist (CRNA) until 2017

Exposed to burn pits in 2003 in Iraq; no other inhalational, toxin or recreational exposures

Pertinent Labs

Non-applicable to case diagnosis

What Imaging Study Could be Performed to Address her Respiratory Symptoms?

Select the applicable ACR Appropriateness Criteria

Revised 2024

American College of Radiology
ACR Appropriateness Criteria®
Chronic Dyspnea-Noncardiovascular Origin

Variant 1: **Adult. Chronic dyspnea. Unclear etiology. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	☢
CT chest without IV contrast	May Be Appropriate	☢☢☢
US chest	Usually Not Appropriate	O
Fluoroscopy chest	Usually Not Appropriate	☢☢☢
MRI chest without and with IV contrast	Usually Not Appropriate	O
MRI chest without IV contrast	Usually Not Appropriate	O
CT chest with IV contrast	Usually Not Appropriate	☢☢☢
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant 2: **Adult. Chronic dyspnea. Suspected COPD). Initial imaging.**

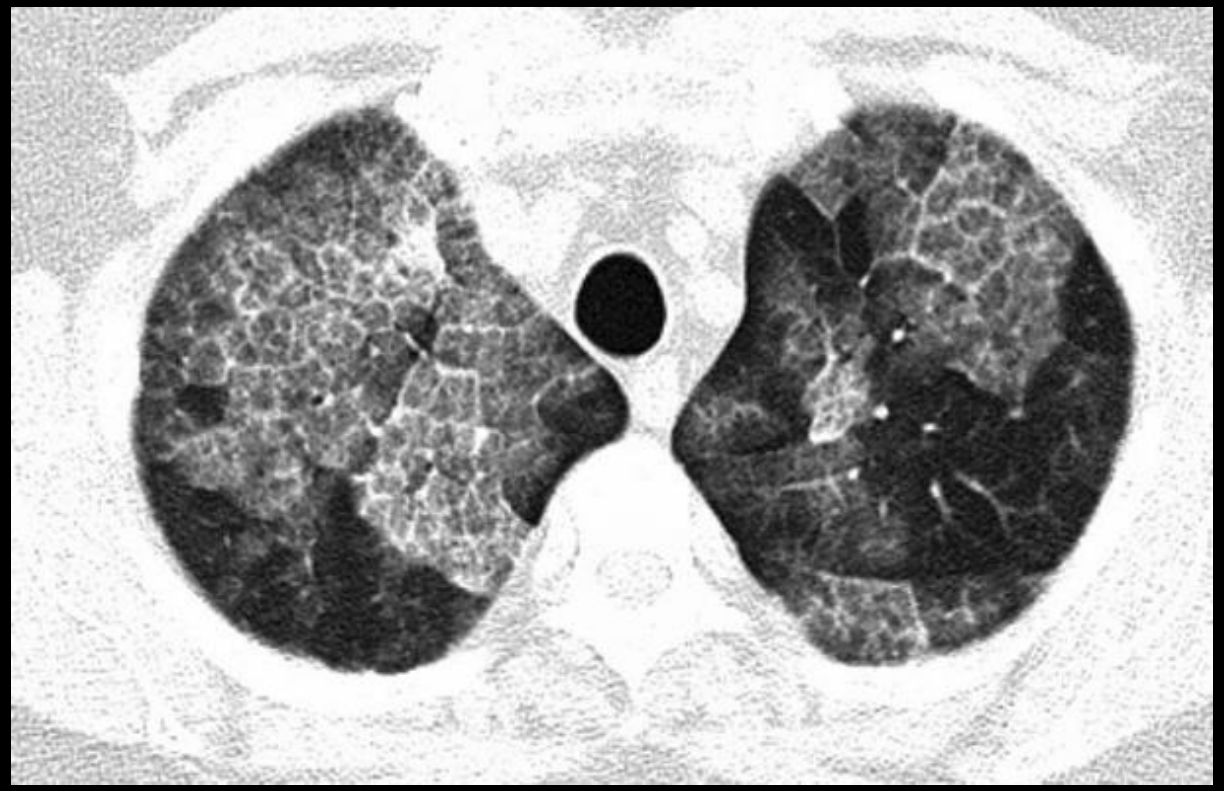
Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	☢
CT chest without IV contrast	Usually Appropriate	☢☢☢
US chest	Usually Not Appropriate	O
Fluoroscopy chest	Usually Not Appropriate	☢☢☢
MRI chest without and with IV contrast	Usually Not Appropriate	O
MRI chest without IV contrast	Usually Not Appropriate	O
CT chest with IV contrast	Usually Not Appropriate	☢☢☢
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
V/Q scan lung	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

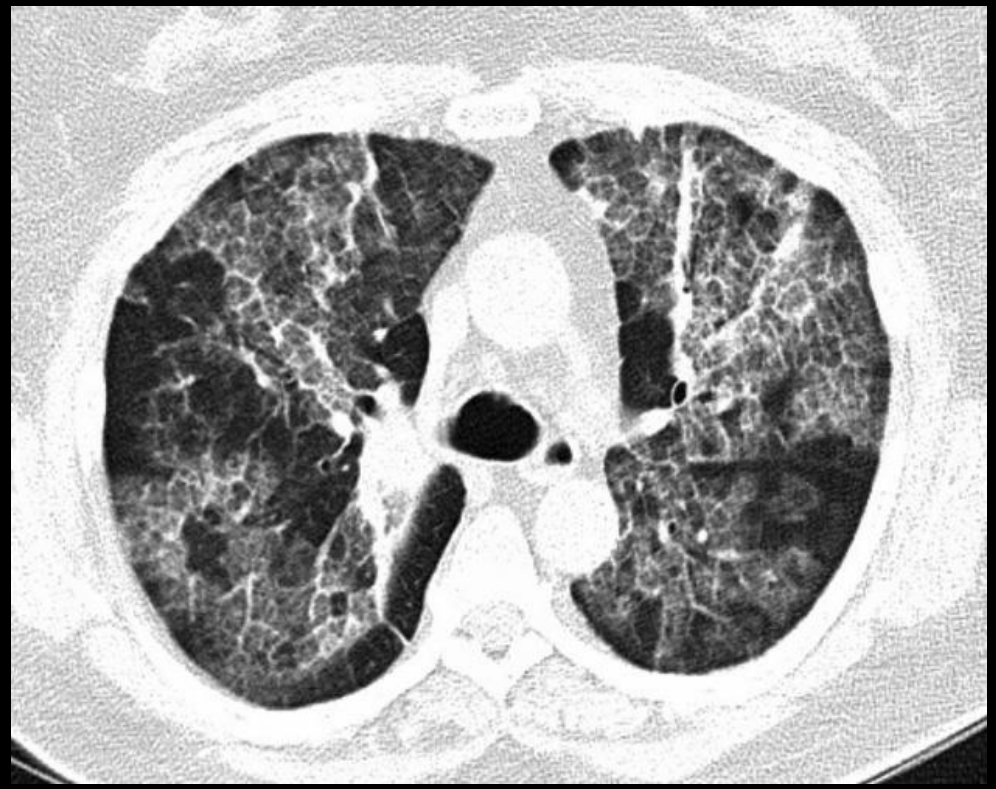
This imaging modality was ordered by the pulmonologist

Initial Imaging: For chronic dyspnea (lasting > 1-month) with suspected pulmonary origin, a chest radiograph (X-ray) is often recommended as the initial imaging study.

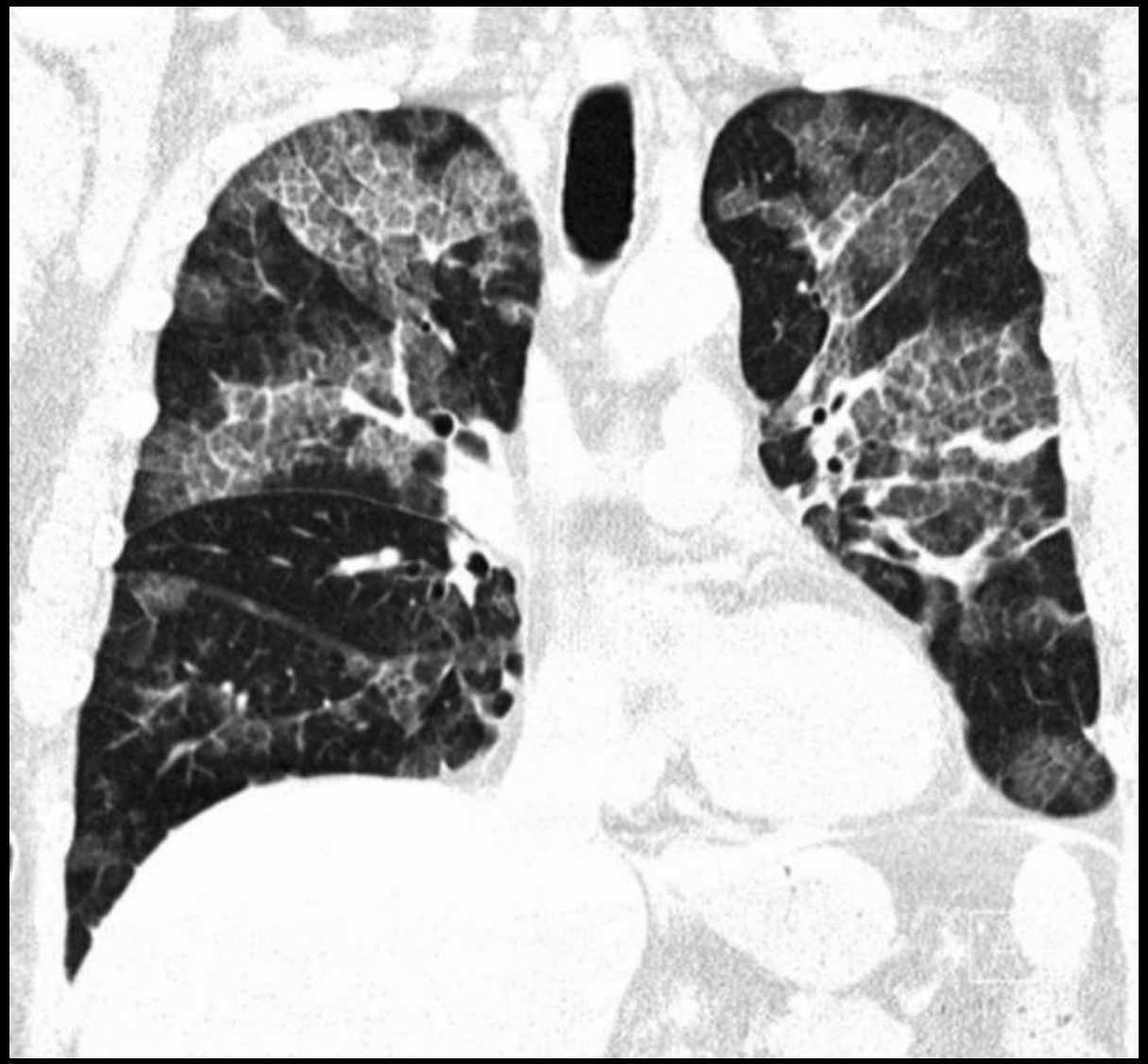
Further Imaging: If the chest radiography is inconclusive or does not provide a clear diagnosis, further imaging with CT (with or without contrast) may be recommended

Findings (unlabeled): Selected Chest CT without Contrast (axial images)



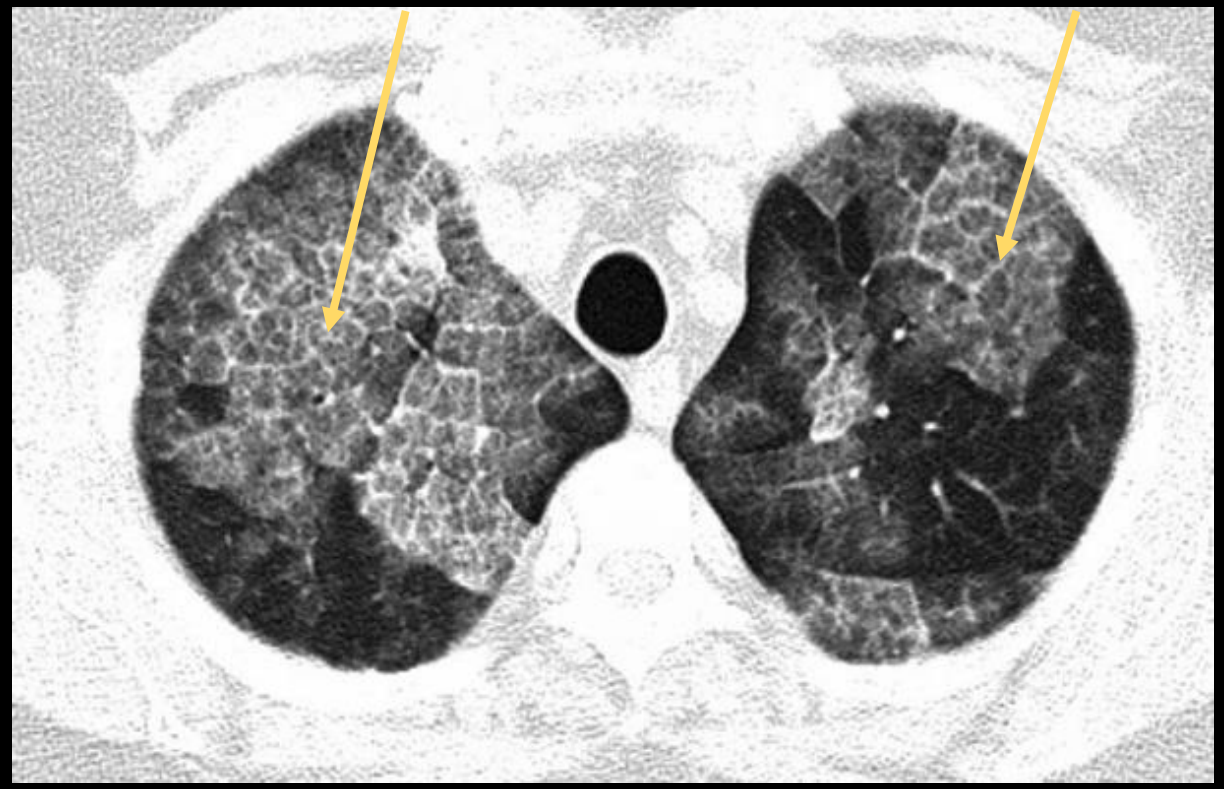


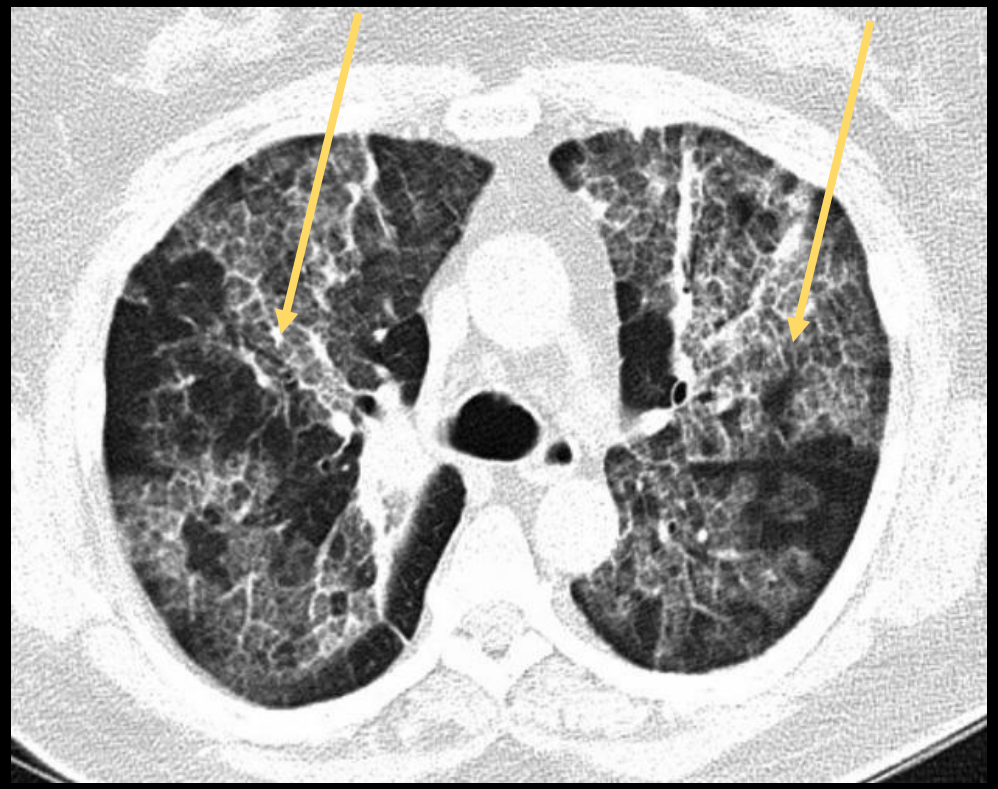
Findings (unlabeled): Selected Chest CT without Contrast (coronal images)



Findings (labeled): Selected Chest CT without Contrast (axial images)

Crazy Paving Pattern: Ground-glass opacities superimposed with interlobular/ intralobular septal thickening, sharply demarcated from adjacent normal lung





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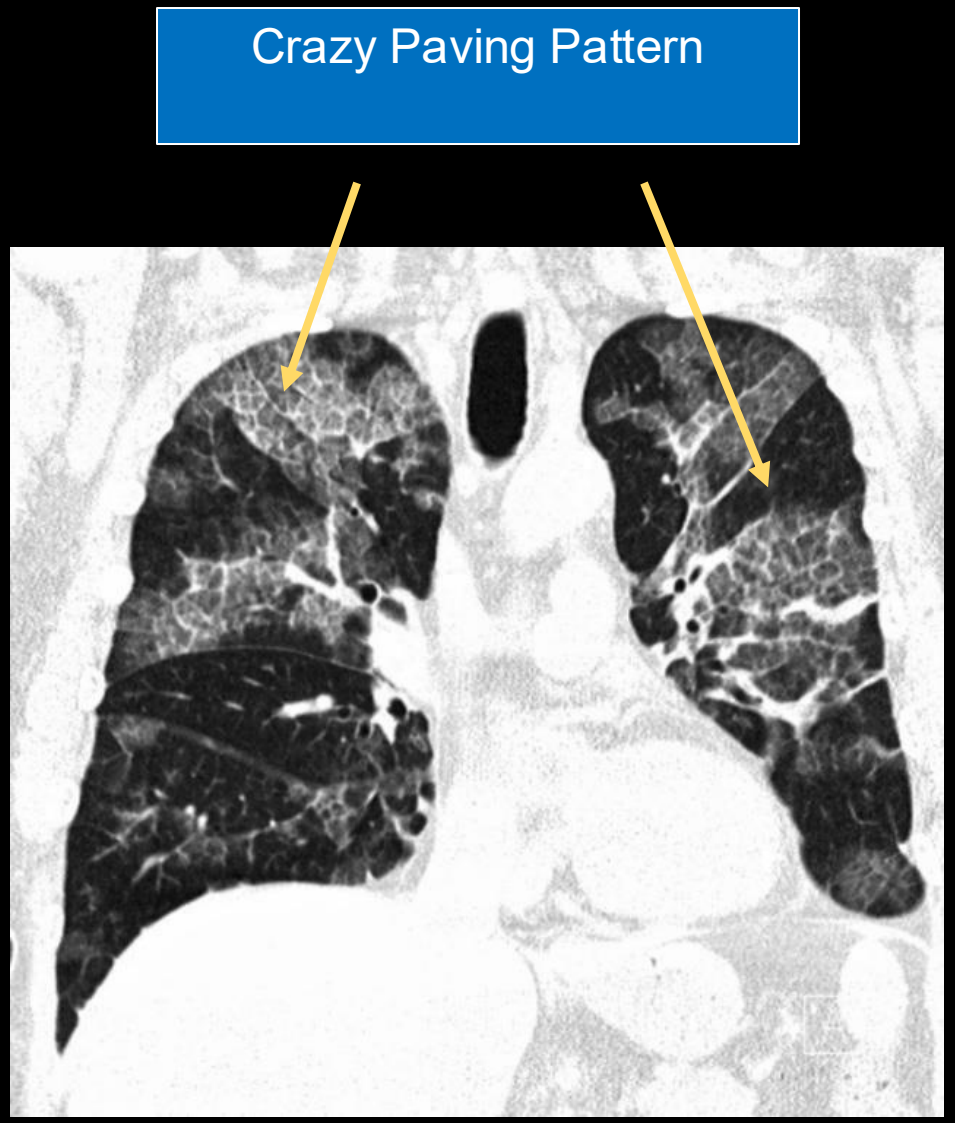

Crazy-Paving Differential Diagnosis

Infectious	Edema	Interstitial Lung Disease	Neoplasia	Hemorrhagic and or Inflammatory	Environmental or Drug-Induced
Pneumocystis *jirovecii* Pneumonia (PJP) - **immunocompromised**	Cardiogenic-CHF; **central distribution**	Pulmonary Alveolar Proteinosis (PAP) – ***Classic cause of crazy paving***	Invasive Mucinous Adenocarcinoma	Diffuse Alveolar Hemorrhage (DAH); Vasculitis, Autoimmune	Drug-Induced Pneumonitis - Amiodarone, Methotrexate, Immunotherapy
Viral Pneumonia - COVID-19, CMV, Influenza	Noncardiogenic (ARDS)-Sepsis, trauma, inhalation injury	Desquamative Interstitial Pneumonia (DIP) – **Smoking-related**	Lymphangitic Carcinomatosis – Metastatic lymphatic spread	Eosinophilic Pneumonia - Acute/chronic	Inhalational Injury - Smoke, chemicals
Atypical Pneumonia - *Mycoplasma pneumoniae*		Non-specific Interstitial Pneumonia (NSIP)- **Autoimmune-associated**			Lipoid Pneumonia – **Aspiration of oily substances**
		Acute Interstitial Pneumonia (AIP) – **Rapid, severe onset**			

Additional Patient Workup

Bronchoscopy with transbronchial biopsy and endobronchial biopsy (EBUS)
Histopathology: Nonspecific inflammation; no malignant cells

Autoimmune workup: Negative

Initial PFTs: FEV_1 98%, DLCO 84%

Video Assisted Thoracic Surgical Biopsy (VATS):

Histopathological report: Suspicious for pulmonary alveolar proteinosis (PAP)

Slides forwarded to Sloan-Kettering- Confirmed diagnosis of PAP

Anti-GM-CSF antibodies: Positive, 422.53 mcg/ml (normal < 8 mcg/ml)

Final Diagnosis:

Pulmonary Alveolar Proteinosis

Case Discussion - Overview

Pulmonary alveolar proteinosis (PAP)
Rare diffuse lung disease characterized by the intra-alveolar accumulation of surfactant-derived, lipoproteinaceous material due to impaired clearance by dysfunctional alveolar macrophages resulting in impaired gas exchange.

Most commonly results from disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF)

Epidemiology:

Prevalence**:** ~7–10 cases per million
Demographics**:** Most commonly adults aged 30-60-year; Slight male predominance
Potential Risk Factors: Cigarette smoking; Various dust and chemical exposures

Types of PAP:

Primary/Idiopathic: ~90%, autoimmune (anti–GM-CSF), occurs in isolation
Secondary: ~ 5-10%, associated with various malignancies, immunodeficiency syndromes; industrial inhalational exposures
Congenital / hereditary: GM-CSF receptor mutations

Clinical Features:

Insidious onset of progressive dyspnea, nonproductive cough, fatigue, weight loss; sometimes mild gelatinous sputum production. Occasional fever, hemoptysis, and digital clubbing, but uncommon and suggests superimposed infection.
Hypoxemia and respiratory failure may develop in advanced case.
Wide clinical spectrum: Asymptomatic to respiratory failure
Caveat: 30% of patients are asymptomatic even with abnormal chest radiography
Caveat: Predisposition to opportunistic infections: *N. asteroides, M. tuberculosis*, PJP, Candida sp., Aspergillus sp., etc.

Case Discussion - Diagnosis

History & Exam:

Assess risk factors: Smoking, occupational exposures, immune or hematologic conditions

Auscultation may reveal “crackles”, “popping” or “bubbling” sounds during inspiration

Labs/PFTs:

Hypoxemia on ABG

Restrictive physiology with reduced diffusion capacity DLCO on PFTs

Serum anti-GM-CSF antibodies-highly sensitive and specific for autoimmune PAP

Imaging

Chest Radiograph:

Initial screening-Bilateral, symmetric, perihilar, and basal airspace opacities with a "bat-wing" or "butterfly" distribution, with relative sparing of the lung periphery, preserved lung volume, and absence of lymphadenopathy or other signs of pulmonary edema

Chest CT and High-Resolution CT (HRCT) Chest:

Hallmark “crazy-paving” pattern-ground-glass opacities with superimposed inter- or intra-lobular septal thickening, sharply demarcated from adjacent normal lung, often with subpleural sparing and lower lobe predominance.

May detect subtle or early disease not conspicuous on chest radiography

Other Work-Up

Bronchoalveolar Lavage (BAL):

Milky effluent with PAS-positive globular proteinaceous material and foamy macrophages; low inflammatory cells

Highly sensitive and can obviate the need for lung biopsy in typical cases

Histopathology (if biopsy performed): Alveoli filled with PAS-positive lipoproteinaceous material; normal interstitium, lamellar bodies seen on EM

Exclusion of secondary causes: malignancy, infection, hematologic disorders

Genetic testing advised in children or adults with non-autoimmune disease

Case Discussion - Treatment

First-line therapy:

Whole-lung lavage (WLL) is the “gold-standard”

For symptomatic or hypoxemic patients
Physically removes alveolar material and improves gas exchange
Typically performed under general anesthesia with a double lumen endotracheal tube, one lung at a time, flushing with isotonic NaCl solution until lung wash return is clear

Second-line therapy:

Inhaled or subcutaneous GM-CSF, pathogenesis-based therapy, particularly for autoimmune PAP

Refractory cases:

Rituximab - targets anti–GM-CSF antibodies
Plasmapheresis - removes anti–GM-CSF antibodies
Lung transplantation-Reserved for adults

Supportive care: O_2 therapy and infection management (e.g., prophylaxis for opportunistic infections like PJP)

Note: Spontaneous remissions have been reported

Patient Outcome

Patient symptoms worsened, necessitating a right whole lung lavage with 33 L of isotonic saline. 3-weeks later a left whole lung lavage with 27 L of isotonic saline was performed The return lavage cannisters are shown below. Patient's symptoms improved after these procedures. Follow-up imaging is pending.

References

1. Da Nam B, Kim TJ, Chung MP, Chung MJ, Kim TS, Lee KS. CT findings in pulmonary alveolar proteinosis: serial changes and prognostic implications. *J Thorac Dis.* 2018 Oct;10(10):5774-5783. doi: 10.21037/jtd.2018.09.86. PMID: 30505485; PMCID: PMC6236152.
2. Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol. 2001 May;176(5):1287-94. doi: 10.2214/ajr.176.5.1761287. PMID: 11312196
3. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. *Lancet Respir Med*. 2018 Jul;6(7):554-565. doi: 10.1016/S2213-2600(18)30043-2. Epub 2018 Feb 1. PMID: 29397349.
4. McCarthy C, Carey BC, Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. *Am J Respir Crit Care Med*. 2022 May 1;205(9):1016-1035. doi: 10.1164/rccm.202112-2742SO. PMID: 35227171; PMCID: PMC9851473.
5. Parker MS. *Diffuse Lung Disease* In *Chest Imaging Case Atlas*. 2nd ed. New York: Thieme; 2012; pp. 523-526.
6. Trapnell BC, *Nakata K, Bonella F, Campo I, Griese M, Hamilton J, Wang T, Morgan C, Cottin V, McCarthy C. Pulmonary alveolar proteinosis. Nat Rev Dis Primers*. 2019 Mar 7;5(1):16. doi: 10.1038/s41572-019-0066-3. PMID: 30846703.
7. Weerakkody Y, Campos A, Röhrich S, et al. Pulmonary alveolar proteinosis [Internet]. Radiopaedia; [cited 2025 Jun 12]. Available from: https://radiopaedia.org/articles/pulmonary-alveolar-proteinosis?lang=us
8. Wołoszczak J, Wrześniewska M, Hrapkowicz A, Janowska K, Szydziak J, Gomułka K. A Comprehensive Outlook on Pulmonary Alveolar Proteinosis-A Review. *Int J Mol Sci*. 2024 Jun 28;25(13):7092. doi: 10.3390/ijms25137092. PMID: 39000201; PMCID: PMC11241585.

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