

JAMA Clinical Challenge

Chest Pain and a Cavitory Lung Mass in a Woman With Diabetes

Alan Koff, MBBS; Maricar Malinis, MD

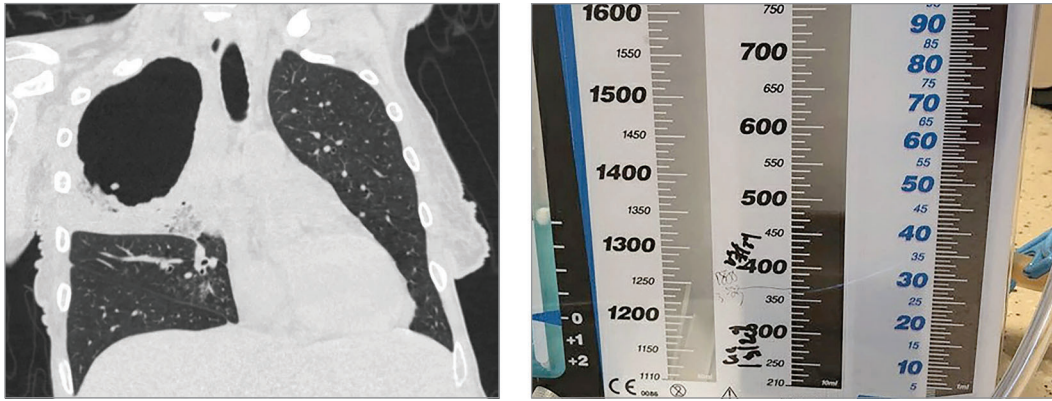


Figure 1. Left, Computed tomography scan of the chest demonstrating large right upper lobe cavitory lesion, layering debris, and bronchial wall thickening. Right, Charcoal-black appearance of the pleural fluid seen in the atrium of the patient's right-side chest tube placed for tension pneumothorax.

A 55-year-old woman from the Southeastern US with a history of smoking, poorly controlled type 2 diabetes mellitus (hemoglobin A_{1c} level, 15.5%), and chronic pain from osteoarthritis treated with inhalational medical marijuana presented with 4 months of productive cough, 22.7-kg (50-lb) weight loss, subjective fevers, and 3 days of worsening chest pain.

Chest computed tomography (CT) showed a large right upper lobe cavitory mass. She was treated empirically with intravenous vancomycin and piperacillin-tazobactam. Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy was performed. Lung tissue was sent for bacterial, fungal, mycobacterial, and *Nocardia* cultures and for histopathology. BAL cultures grew 100 colony-forming units (CFUs)/mL of group B streptococci and 1 CFU/mL of *Aspergillus niger*. Results of acid-fast bacilli (AFB) smear and GeneXpert MTB/RIF testing were negative. Voriconazole was added to her treatment. Transbronchial biopsy histopathology showed acute and chronic inflammation, granulation tissue and necrosis, and negative fungal and AFB stains.

Two weeks later, the patient reported worsening right-sided chest pain provoked by palpation, right arm movement, and deep inspiration. Repeat chest CT demonstrated cavitory mass enlargement with possible pleural invasion (Figure 1, left). She developed hypoxemia and required intubation. A right-sided tension pneumothorax developed and required emergency chest tube placement, which yielded charcoal-colored pleural fluid (Figure 1, right).

WHAT WOULD YOU DO NEXT?

- A. Change antimicrobial therapy to meropenem and vancomycin
- B. Change voriconazole to liposomal amphotericin B
- C. Consult radiation oncology immediately
- D. Perform right upper lobe resection

Diagnosis

Fungal empyema

What to Do Next

- D. Perform right upper lobe resection

The key to the correct diagnosis was recognizing that the tension pneumothorax after intubation suggested rupture of the right-sided cavitory lesion into the pleural space. The charcoal-colored pleural fluid is characteristic of the melanin-producing *Aspergillus niger*. A change in antimicrobial therapy would not be sufficient to manage this complication. Voriconazole is favored over amphotericin B for *Aspergillus spp*. Without malignancy, radiation therapy is not indicated.

Discussion

The differential diagnosis of a cavitory lung mass includes infection, malignancy, or autoimmune disease. In patients with immunosup-

pression from diabetes, infection should be considered. Fevers, weight loss, and chronic productive cough are consistent with *Mycobacterium tuberculosis* or nontuberculous mycobacteria, but negative AFB smears and Xpert MTB/RIF results (for *Mycobacterium tuberculosis*) from the BAL makes this less likely. Prior residence in the Southeastern US is associated with cavitory histoplasmosis or blastomycosis, showing small intracellular yeast or broad-based budding yeast on histopathology, respectively. The lungs may be the primary site of mold infections (eg, *Aspergillus* or *Mucorales spp*), which cause significant morbidity and mortality. Mold in the sputum may be considered a contaminant but should be further evaluated in patients with a cavitory lung lesion or underlying risk factors. Pulmonary cavitation may be caused by a necrotizing bacterial infection (eg, *Staphylococcus aureus*, *Klebsiella pneumoniae*, anaerobes) or bacterial superinfection of existing cavities. Noninfectious causes of cavitory lung disease

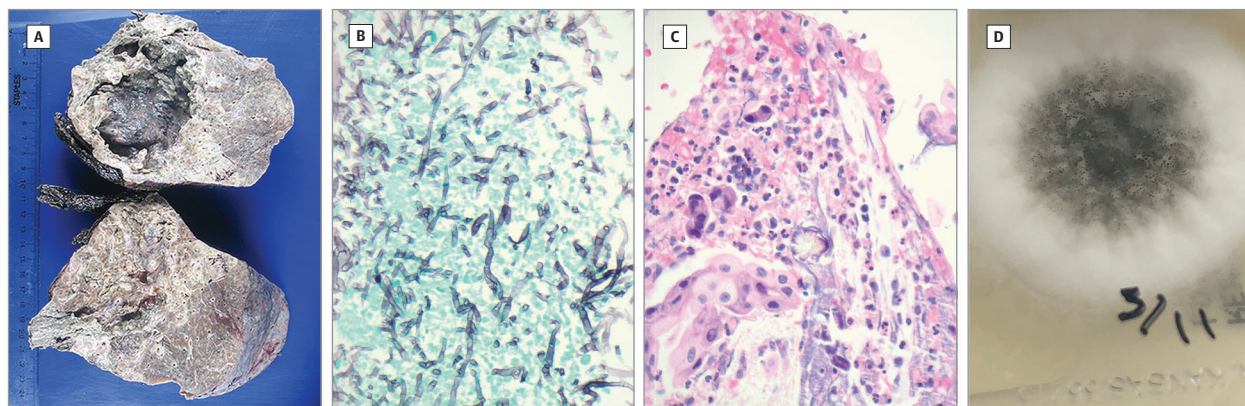


Figure 2. A, Right upper lobe resection with cavity hyperpigmented lung mass. B, Fungal hyphae on surgical pathology (Gomori methanamine silver, original

magnification $\times 40$). C, Calcium oxalate crystal produced by *Aspergillus niger*. D, Growth of melanin-pigmented *Aspergillus niger* on Sabouraud dextrose media.

include malignancy (eg, primary lung cancer, metastatic squamous cell carcinoma), granulomatosis with polyangiitis, or thromboembolism with pulmonary infarction.

Pulmonary aspergillosis is more common in the setting of prolonged neutropenia, high-dose corticosteroids, or lung transplantation but should also be considered in patients with chronic lung disease due to cigarette smoking, inhaled marijuana use, malnutrition, alcohol abuse, or poorly controlled diabetes. This patient developed subacute invasive pulmonary aspergillosis (SIPA) due to *Aspergillus niger*. Diagnosing SIPA requires at least 3 months of symptoms (eg, productive cough, weight loss, fevers), a cavitary lung lesion with or without a fungus ball (intracavitary rounded consolidation), and microbiologic evidence such as an elevated serum *Aspergillus* IgG level, positive respiratory cultures, or lung histopathology demonstrating fungal hyphae. Historically, itraconazole was the drug of choice, but voriconazole has more predictable drug levels and an improved safety profile.^{2,3} These drugs inhibit P450 enzymes and are also metabolized by P450 enzymes. Therefore, potential drug interactions must be considered. Monitoring serum drug concentrations is recommended to help ensure that levels remain in the therapeutic window.² Newer triazole antifungals such as posaconazole and isavuconazole are increasingly prescribed for invasive aspergillosis, although data for treating SIPA are limited. Amphotericin B or the echinocandins (eg, anidulafungin) may be considered for resistant or refractory infection.^{2,3} Treatment duration

is often greater than 6 months—sometimes years. Optimal duration varies depending on the rate of clinical improvement and surgical intervention.³ Clinical monitoring of symptoms and serial imaging alone may be reasonable for asymptomatic patients without significant respiratory impairment.³ While surgery may be curative when infection is completely resected, relapse is common.⁴ Because of risks associated with operative treatment, resection is typically reserved for those with treatment intolerance, refractory disease, refractory hemoptysis, or local complications such as rupture into the pleural space.^{3,4}

Patient Outcome

Due to her rapid decline and concern for empyema, the patient underwent emergent right upper lobe resection (Figure 2A). Pathology showed acute necrotizing pneumonia and invasive fungal hyphae (Figure 2B), with calcium oxalate crystals consistent with *Aspergillus niger* (Figure 2C). Morphologic appearance on Sabouraud dextrose media was diagnostic of *Aspergillus niger* (Figure 2D). Serum (1-3)- β -D-glucan and galactomannan were undetectable. BAL galactomannan index was 5.27 (normal, <0.5). *Citrobacter freundii* and *Klebsiella oxytoca* were isolated from the pleural fluid, suggesting possible superinfection. For fungal empyema, she was treated with voriconazole and anidulafungin for 2 weeks and discharged to a skilled nursing facility for rehabilitation and continued receipt of voriconazole.

ARTICLE INFORMATION

Author Affiliations: Yale School of Medicine, Section of Infectious Diseases, Department of Medicine, New Haven, Connecticut.

Corresponding Author: Maricar Malinis, MD, Yale School of Medicine, PO Box 208022, New Haven, CT 06520-8022 (maricar.malinis@yale.edu).

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Submissions: We encourage authors to submit papers for consideration as a JAMA Clinical Challenge. Please contact Dr McDermott at mdm608@northwestern.edu.

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