Case in Point

Nocardia Bacteremia Associated With Pulmonary Alveolar Proteinosis

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This patient developed a rare pulmonary disease that left her vulnerable to the opportunistic pathogen *Nocardia nova.*

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disease, in which abnormal amounts of surfactant-rich material accumulate in the alveoli and interfere with gas exchange. Clinically, PAP is characterized by the insidious onset of exertional dyspnea and cough.[1] Less common symptoms include fatigue, weight loss, and fever, which typically occur if secondary infection is present.[1] With only approximately 400 cases reported in the literature since it was first described in 1958, PAP remains a rare cause of respiratory failure.[2]

Nocardia asteroides and *Mycobacterium tuberculosis* represent the most commonly associated infections, while the presence of *Mycobacterium avium-intracellulare* also has been reported in individuals with PAP.[3] Increased awareness of PAP, its associated complications, and its unique presentations may improve clinical outcomes, given its favorable response to treatment.[1]

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INITIAL PRESENTATION

A 43-year-old woman presented to the emergency department of a local community hospital for evaluation of her cough and progressive dyspnea of 4 months' duration. She reported that the dyspnea was mild, and that the cough was productive of yellow sputum. She denied having a fever, night sweats, chills, or hemoptysis. The patient had a history of breast cancer, which was diagnosed 4 years prior to presentation, and was treated with 4 cycles of doxorubicin and cyclophosphamide.

Notably, results of an open lung biopsy done at the community hospital were interpreted as "fibrosis with chronic inflammation." Given these pathologic findings, the hospital started the patient on oral prednisone 60 mg/day. She was transferred to our medical center approximately 4 days thereafter, when her symptoms showed no appreciable improvement.

Upon transfer, initial radiographs of her chest revealed predominantly bilateral basilar alveolar infiltrates and a right upper lobe interstitial infiltrate (Figure 1). Subsequent computed tomography scan of her chest revealed extensive infiltrates in both an interstitial and an alveolar pattern (Figures 2a and 2b).

Upon admission, arterial blood gas analysis revealed a slightly elevated

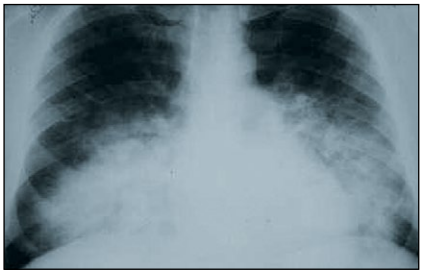
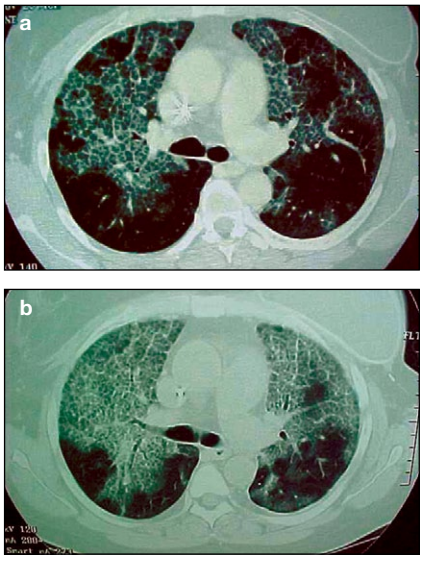


Figure 1. Initial radiograph of patient's chest, revealing predominantly bilateral basilar alveolar infiltrates and a right upper lobe interstitial infiltrate.



Figures 2a and 2b. Initial computed tomography scan of patient's thorax, revealing infiltrates in both an interstitial and alveolar pattern.

pH of 7.48 (reference, 7.35 to 7.45), a low carbon dioxide level of 26 mm Hg (reference, 35 mm Hg to 45 mm Hg), and a slightly elevated oxygen level of 105 mm Hg (reference, 80 mm Hg to 100 mm Hg) on 4 liters of oxygen by nasal cannula. Laboratory evaluation of the patient was remarkable only for an elevated white blood cell count (27.4 k/µl), with 93% segmented neutrophils (Table).

Oral prednisone was discontinued and intravenous methylprednisolone 125 mg every 6 hours was initiated; but, again, the patient's symptoms failed to improve after 4 days on this regimen.

Five days after transfer, the microbiology laboratory reported beaded and branching gram-positive rods (Figures 3 and 4) on a blood culture performed on admission, which also stained positive on modified acid-fast stain (Figure 5). The organism was identified as *Nocardia nova* and, based on the severity of the organism (Figure 6), the patient was started on trimethoprim/sulfamethoxazole. Her symptoms failed to show any improvement after 4 days of therapy, however.

Due to the accumulation of toxic sulfamethoxazole levels and the patient's clinical failure to respond to treatment, this medication was discontinued. Subsequent bronchoscopy was performed and yielded a bronchoalveolar lavage fluid that settled in a layered pattern (Figure 7). Analysis of the fluid revealed an abundance of coarsely granular eosinophilic macrophages and cell debris, which stained periodic acid-Schiff (PAS) positive, confirming a diagnosis of PAP (Figures 8a to 8c).

The patient was treated with whole-lung lavage (Figure 9), which demonstrated progressive clearing of her abnormal bronchial fluid, and was started on minocycline 100 mg

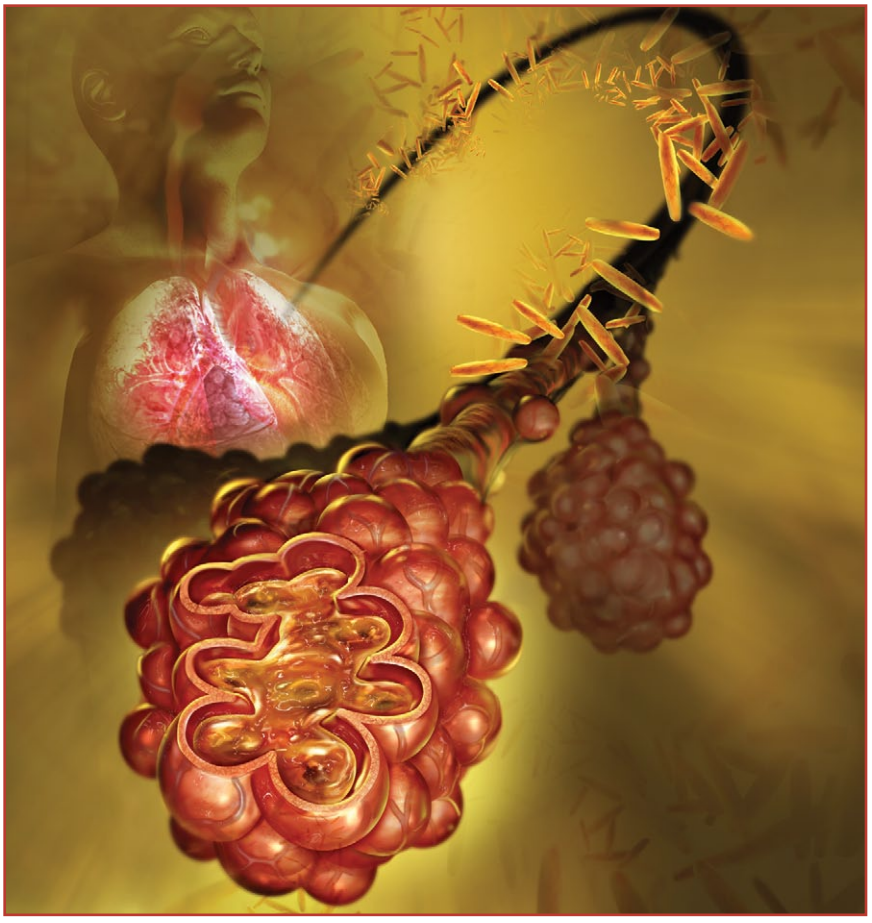


Table. Patient's initial laboratory results upon transfer

Laboratory test	Patient's result	Reference range
White blood cell count, k/µl	27.4	4.0-10.0
Neutrophils, %	93	45-70
Antinuclear antibody	Negative at 1:40 dilution	Negative
Erythrocyte sedimentation rate, mm/h	32	0-20
Complement 3 level, mg/dL	121	88-201
Complement 4 level, mg/dL	19	16-47
HIV-1 and HIV-2 antibodies	Negative	Negative
Rheumatoid factor, IU/mL	< 20	< 20
Purified protein derivative	Negative	Negative

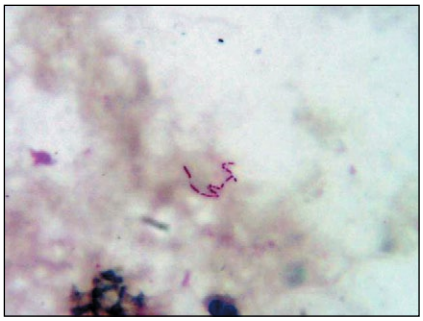


Figure 3. Gram stain of blood culture, showing beaded and branching gram-positive rods.

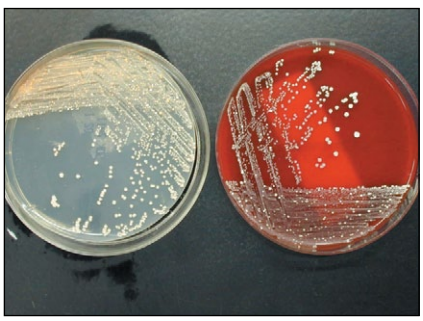


Figure 4. Blood culture growth on agar plate.

twice daily prior to discharge from her 49-day hospital stay.

DISCUSSION

More than 90% of PAP cases are thought to be acquired, and the prevalence is estimated to be 0.37 cases per 100,000 people.[1] PAP has been described in 3 forms: The acquired form is idiopathic; the congenital form is caused by genetic mutation; and the third form is secondary PAP, which occurs as a consequence of such conditions as immunosuppression, infectious disease, and hematologic malignancy.[1]

The median age at time of diagnosis is 39 years, and males are thought to be affected approximately twice as often as females, due to a higher prevalence of smoking in men.[1,2] The most common symptoms at time of presentation include progressively worsening exertional dyspnea in addition to cough.[1,2] Other associated symptoms include fever, weight loss, chest discomfort, and hemoptysis, but these are much less common unless a secondary infection is present.[1,2] Health care professionals speak to the clinical finding of inspiratory crackles as the most common symptom reportedly observed.[1,2]

Bronchoscopy may aid in confirming a diagnosis of PAP, but the gold standard is open lung biopsy.[1,2] While whole-lung lavage plays an important role in the treatment of PAP, patients may require subsequent lavage due to recurrence of the disease.[1,2] Current research also is evaluating the role of granulocyte macrophage colony-stimulating factor (GM-CSF) in treating patients found to have PAP.[1,2,4]

Nocardia infection has been noted increasingly as a consequence of immunosuppression.[5] Estimates suggest approximately 1,000 new cases every year in the United States.[6] Patients with a history of organ transplantation, steroid use, or malignancy are at the highest risk of infection by this pathogen.[5,7-9] In our patient, steroid therapy may have increased her risk of infection; however, her history of malignancy was not likely a contributing factor in the development of nocardiosis. While the lung is the portal of entry in most cases of nocardiosis, hematogenous dissemination rarely occurs.[5,10] We believe this to be the first case of *Nocardia* bacteremia associated with PAP.

A review of systemic *Nocardia* infections by Kontoyiannis and colleagues demonstrated that 86% of patients with nocardiosis had an underlying chronic disease, with 70% receiving chronic immunosuppression.[10] Of all patients with systemic nocardiosis, the lung was the most

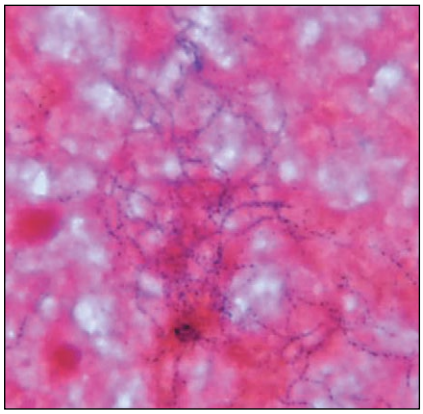


Figure 5. Modified acid-fast stain of blood culture, showing positive reactivity.

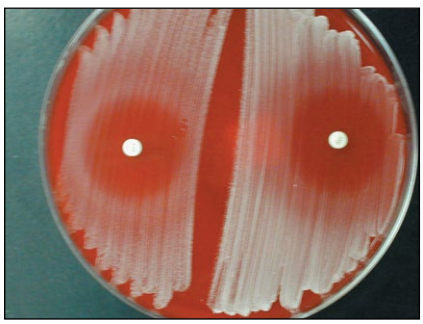


Figure 6. Antibiotic sensitivity of *Nocardia* on agar plate.

frequent (64%) concomitant site of infection, and *N asteroides* was the most common (77%) species causing infection.[10] Blood cultures usually become positive for *Nocardia* between 1 and 12 weeks after onset of infection, with a median of 3 weeks.[10]

IN CONCLUSION

PAP is a diffuse lung disease characterized by the accumulation of amorphous, PAS-positive, lipoproteinaceous material in distal air spaces.[1,2] Macrophage dysfunction and GM-CSF play important roles in the initiation and propagation of the disease.[1,2] Alveolar macrophage and type II pneumocyte cell clearance mechanisms are progressively overwhelmed

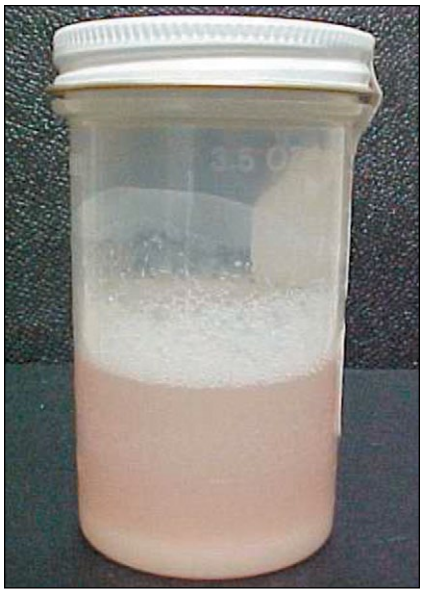
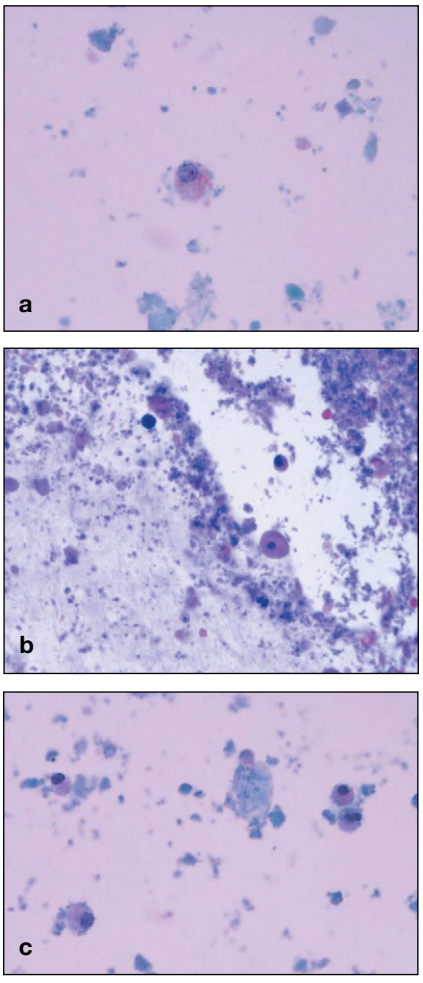


Figure 7. Initial bronchial fluid obtained at time of bronchoscopy.

by the accumulation of surfactant-rich material, resulting in impaired phagocytosis and phagolysosome fusion.[1,2] This impaired function results in an increased risk of superinfection in PAP patients by opportunistic organisms, such as *Nocardia*, *Mycobacterium*, and endemic fungi.[1-3]

Our patient likely developed PAP prior to her *Nocardia* infection. The immunosuppressive therapy used in her treatment course undoubtedly predisposed her to infection with such opportunistic pathogens. Interestingly, the species of *N nova,* identified as the pathogen in this case, is rare in causing systemic infection among *Nocardia* organisms.[10] One wonders whether this is an indication of an emerging theme in cases of *Nocardia* causing systemic infection or simply an isolated event. Regardless, the patient's prolonged hospital stay placed her in a much different environment than that found in the community, which could have been the reason for such a rare pathogen being identified.



Figures 8a to 8c. Microscopic analysis of bronchial fluid, confirming a diagnosis of pulmonary alveolar proteinosis.

In summary, a diagnosis of *Nocardia* should be entertained in those with PAP when the clinical presentation suggests superinfection.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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Figure 9. Five 2,500-cc containers, showing progressive clearing of the abnormal bronchial fluid seen in pulmonary alveolar proteinosis.

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