



A 46-Year-Old Man With Seizures, Brain Lesions, and Pulmonary Infiltrates

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CHEST 2012; 141(1):265–269

A 44-year-old man with no medical history presented with multiple new-onset seizures during 1 week. He denied tobacco, alcohol, or illicit drug use. He worked for 15 years spraying pesticides and herbicides on farms. On presentation, the patient was actively seizing. He was treated with antiepileptic medications and intubated for airway protection.

Physical Examination

His vital signs were normal. Physical examination was unremarkable except for crackles at the lung

bases. Neurologic examination was limited by sedation. The WBC count was 14,100/ μ L, and the remainder of his CBC, electrolytes, and renal and liver function results were normal. MRI of the brain showed multiple lesions in the right occipital lobe, left temporal lobe, and bilateral frontal and parietal lobes (Fig 1).

Laboratory Findings

A transesophageal echocardiogram was negative for vegetations and shunt. Blood cultures were negative. Chest radiograph revealed atelectasis vs consolidation at the lung bases. CT scan of the chest is shown

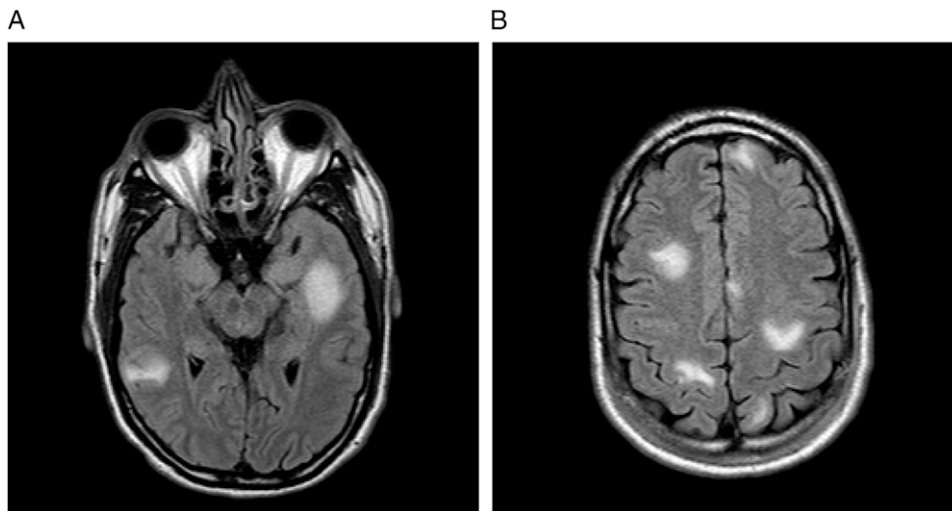


FIGURE 1. A, B, Two views of a brain MRI demonstrating multiple focal white matter lesions with some cortical involvement.

Manuscript received June 4, 2011; revision accepted June 16, 2011.

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Funding/Support: This work was supported by the National Institutes of Health [grant HL103772] (to Dr Zemans).

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DOI: 10.1378/chest.11-1397

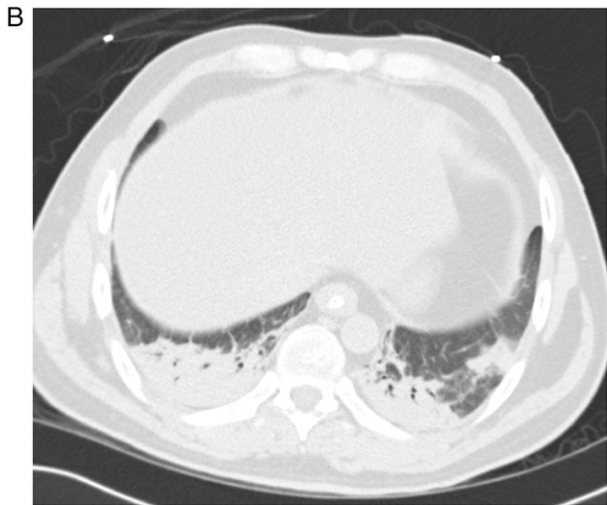
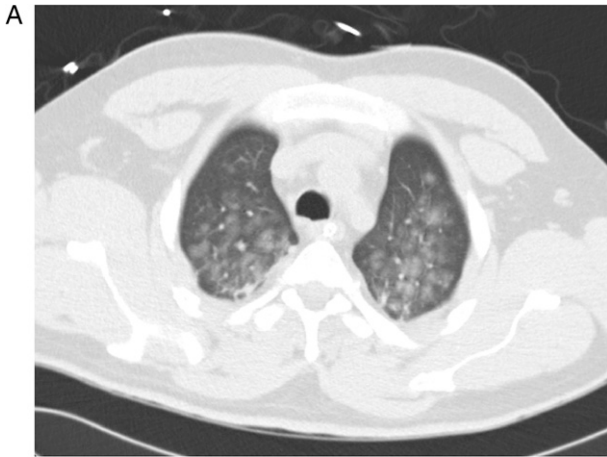


FIGURE 2. A, Chest CT scan demonstrating patchy ground glass in the upper lobes bilaterally. B, Chest CT scan demonstrating consolidation in the lower lobes bilaterally.

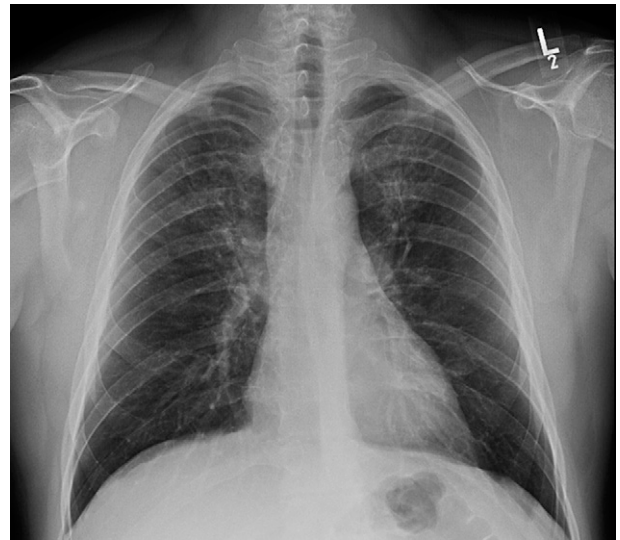


FIGURE 4. Chest radiograph 2 weeks later showing resolution of the lower-lobe consolidation.

in Figure 2, and abdominal CT scan was normal. BAL cultures were negative, and no malignant cells were present. Brain biopsy specimen revealed an abscess with numerous branching, filamentous bacteria consistent with *Nocardia* species (Fig 3). HIV antibody was negative, and immunoglobulin levels were normal.

The patient was treated with a 1-year course of trimethoprim/sulfamethoxazole for cerebral nocardiosis, a 14-day course of amoxicillin/clavulanate for aspiration pneumonia, and antiepileptics. Chest radiograph 2 weeks later showed resolution of the lower lobe consolidation (Fig 4). One year later, MRI

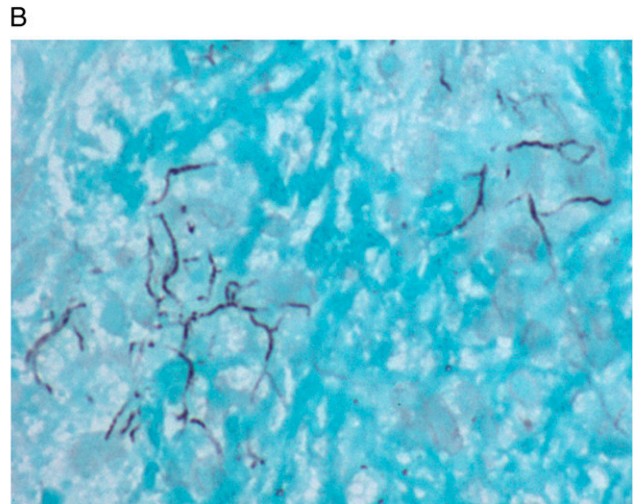
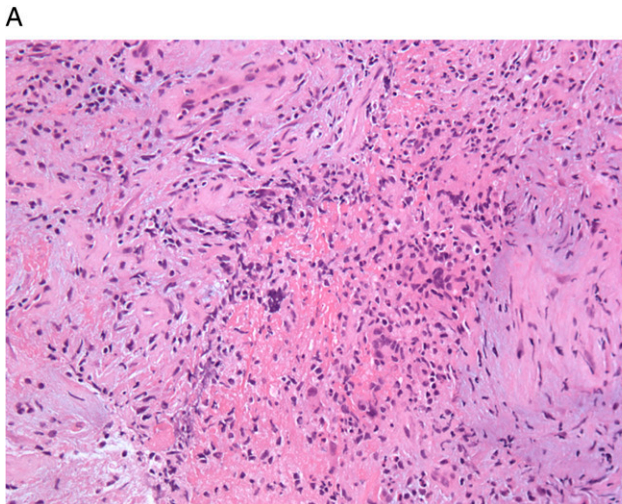


FIGURE 3. A, Brain biopsy specimen demonstrating an abscess with central necrosis and surrounding multinucleated giant cells (hematoxylin-eosin stain, original magnification $\times 20$). B, Brain biopsy specimen demonstrating numerous branching, filamentous bacteria consistent with *Nocardia* species within the necrotic center (Grocott methenamine silver, original magnification $\times 60$).

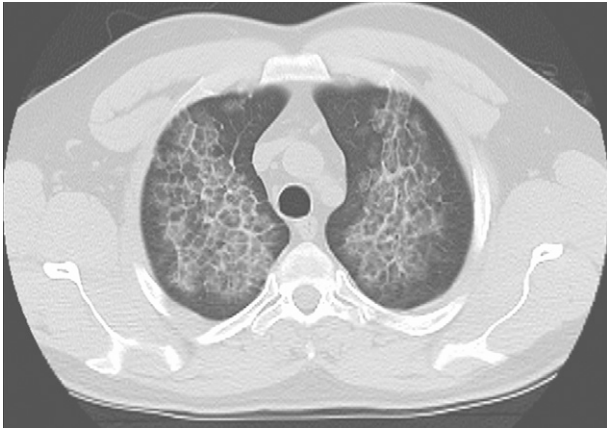


FIGURE 5. Chest CT scan demonstrating upper-lobe airspace opacities increased but in the same distribution as 1 year prior and now accompanied by septal thickening in a “crazy paving” pattern.

revealed resolution of the brain lesions, but dyspnea and cough productive of white sputum developed in the patient. His oxygen saturation was 94% on room air, and lungs were clear to auscultation. Pulmonary function testing revealed normal lung volumes and flows and a diffusing capacity of 78% predicted. Chest CT scan is shown in Figure 5.

What is the diagnosis?

DISCUSSION

BAL revealed milky fluid containing periodic acid-Schiff (PAS)-positive proteinaceous material with foamy macrophages, confirming the diagnosis of pulmonary alveolar proteinosis (PAP). Anti-granulocyte macrophage colony-stimulating factor (GM-CSF) antibodies were detected in the serum at 116.7 $\mu\text{g/mL}$ (normal, $< 3 \mu\text{g/mL}$). PAP is a rare disease caused by abnormal accumulation of surfactant in the lung. It presents with the insidious onset of shortness of breath sometimes accompanied by cough, weight loss, and fatigue. Physical examination may be normal, or mild crackles may be present. The subtle and nonspecific signs and symptoms often lead to delayed diagnosis. Pulmonary function testing may reveal mild restrictive disease with a decreased diffusing capacity. Chest radiograph typically reveals bilateral, patchy alveolar filling but is insensitive for detecting mild disease. CT scan findings include patchy ground glass with superimposed thickened interlobular septae, resulting in a “crazy paving” pattern. The diagnosis may be made from BAL fluid, which is milky, reflecting the presence of lipoproteinaceous material that is PAS positive and contains foamy macrophages. Open lung biopsy specimens reveal PAS-positive proteinaceous material in the airspaces with normal alveolar septae.

PAP is classically divided into three subgroups based on the pathogenesis of disease: primary, congenital, and secondary. The most common form in adults is primary (or autoimmune) PAP, which is caused by neutralizing antibodies against GM-CSF. These antibodies impair macrophage development, leading to decreased catabolism of surfactant. Congenital PAP is caused by mutations in the genes for surfactant proteins or GM-CSF receptors. Secondary PAP develops in the setting of underlying conditions, including hematopoietic malignancies and immunodeficiency syndromes, both of which may be associated with a functional macrophage deficiency. PAP due to inhalational exposures also is categorized as secondary PAP, although some have challenged the classic distinction between primary (autoimmune) PAP and secondary (antibody negative) PAP due to occupational exposures, reasoning that inhalational agents may expose sequestered antigens and trigger autoimmunity. For instance, this patient was likely predisposed to autoantibody development and PAP by exposure to insecticides, an association which has been previously reported.

The anti-GM-CSF antibodies that develop in primary PAP impair the antimicrobial functions of mac-

rophages and neutrophils, leading to susceptibility to opportunistic infections, including endemic fungi, mycobacteria, and classically, *Nocardia* species. *Nocardia* infection usually develops in the lungs in the setting of previously diagnosed PAP. However, the initial clinical manifestation of PAP can be *Nocardia* infection; isolated CNS nocardiosis has been reported in patients with PAP as well.

Although spontaneous resolution of PAP is described, most patients are treated with physical removal of the lipoproteinaceous material through large-volume lung lavage. Whole-lung lavage is highly effective in improving symptoms, oxygenation, and radiographic infiltrates, and likely has a survival benefit; however, symptoms and infiltrates often recur, and repeat lavages may be necessary. Autoimmune PAP can be treated with inhaled GM-CSF, which is effective in $\sim 69\%$ of patients and generally is well tolerated. Secondary PAP usually responds to treatment of the underlying disease. The overall prognosis of primary PAP is favorable because the disease typically becomes quiescent to the extent that continued therapy is not necessary. Occasionally, pulmonary fibrosis may develop. The overall 5-year survival rate of primary PAP is upwards of 90%, but mortality is well described from PAP and its complications, such as CNS nocardiosis, which itself carries a mortality rate of up to 44%.

Clinical Course

The extended course of this case demonstrates both the characteristic features of PAP and the challenges in making the diagnosis and, therefore, merits brief discussion. When the patient presented with seizures and brain lesions, a thorough search for embolic and metastatic disease (echocardiogram, full-body CT scan, and bronchoscopy) was undertaken. The initial brain biopsy specimen findings of nocardiosis prompted consideration of predisposing conditions and a pulmonary portal of entry, but given the absence of immunodeficiency and negative BAL cultures, the pulmonary infiltrates were reasonably attributed to a postseizure aspiration pneumonia. Treatment was directed accordingly, and apparent radiographic improvement supported this working diagnosis. The clinical presentation of symptomatic airspace disease 1 year later provided strong evidence that a chronic pulmonary process was present and forced the clinicians to revisit the previously constructed cause-and-effect sequence. The repeat presentation—now textbook in its features—allowed the treating physicians to recognize that PAP was the underlying condition that explained the patient’s multisystem illness.

The patient underwent whole-lung lavage after the clinical and radiographic manifestations of the

disease progressed further. His symptoms, infiltrates, and diffusing capacity improved, and he was maintained on inhaled GM-CSF.

Clinical Pearls

1. *The insidious onset and the subtle signs, symptoms, pulmonary function, and chest radiograph findings of PAP may result in a delay in diagnosis.*

2. *In PAP, autoantibodies to GM-CSF impair macrophage function, leading to both a defect in surfactant clearance and impaired host defense, which predisposes to opportunistic infections, such as nocardiosis.*

3. *Patients with PAP may present with infection; PAP should be considered in the search for predisposing conditions in a patient with nocardiosis or other opportunistic infections.*

4. *The classic distinction between primary (autoimmune) PAP and secondary (antibody negative) PAP due to occupational exposures can be misleading because inhaled toxins may expose sequestered antigens and trigger autoimmunity.*

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Other contributions: We thank James Ellis, MD, and Dennis Lyu, MD, for thoughtful discussions.

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