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Menace Elbow: Disseminated Nocardiosis

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PRESENTATION

A vivid argument can be made against presumptive diagnosis of a serious disease based on clinical and radiologic findings. Our patient's case emphasizes the importance of a confirmatory tissue sample.

An active 86-year-old veteran presented to the emergency department with chronic right elbow pain. Two months prior to admission, he had presented to another hospital with the same complaint. At that time, magnetic resonance imaging (MRI) showed an effusion with possible osteomyelitis. An aspirate from the elbow was added to thioglycolate broth, and this test revealed gram-positive rods. He was treated with vancomycin for 4 weeks and then followed with a regimen of amoxicillin clavulanate and doxycycline for 2 more weeks. When the pain persisted, he presented to our hospital.

Eighteen months before admission, the patient was evaluated at another hospital for a nontender right axillary subcutaneous mass. Computed tomography (CT) of the chest and abdomen demonstrated a 4.5-cm right upper lobe amorphous mass, a 3.3-cm centrally necrotic right axillary mass, and 1 enlarged right hilar lymph node. A core biopsy of the axillary mass revealed keratinized pleomorphic squamous epithelial cells. Immunohistochemical staining identified tumor protein P63, a marker consistent with squamous cell cancer; the specimen was also positive for the programmed cell death ligand-1 (PD-L1).

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Bronchoscopy with lung biopsy was deferred, but the patient was given a presumptive diagnosis of metastatic lung squamous cell cancer. MRI and positron emission tomography of the brain proved negative for additional metastases. The patient received palliative chemoradio-therapy for 4 months. Six months after treatment, he underwent a month of immunotherapy with pembrolizumab, a drug aimed at the programmed cell death path-way. He then received prolonged steroid treatment for pneumonitis, a condition that can result from treatment with pembrolizumab.

The patient's medical history also included large granular lymphocytic leukemia, for which he was being observed, and resected skin squamous cell cancer. He had been a minimal smoker and had no history of asbestos exposure. On admission to our hospital, his medications were amiodarone, metoprolol, and latanoprost eye drops.

ASSESSMENT

On physical examination, the patient was afebrile, alert, and in no distress. His vital signs were stable, and he had a tender, nonerythematous right elbow with a limited range of motion. An indurated scaly plaque measuring 6 × 3 cm was noted in his right pectoral region (Figure 1).

Laboratory findings were pertinent for a total leukocyte count of 10,000 cells/ μ L, a C-reactive protein level of 76 mg/L, and an erythrocyte sedimentation rate of 89 mm/hour. Results from a blood chemistry screen and liver function tests were within normal limits. The patient's right elbow was aspirated in the emergency department. The procedure yielded thick, purulent synovial fluid (Figure 2). He then underwent urgent arthrotomic drainage, and an empiric regimen of high-dosage trimethoprim/ sulfamethoxazole with meropenem was initiated.

DIAGNOSIS

Nocardia niwae with a 16S sequence identical to strain W9241 (GenBank, National Institutes of Health, accession number, 116801.1) was isolated from the synovial fluid. The organism was eventually reported as susceptible to linezolid, imipenem, and trimethoprim-sulfamethoxazole.¹ Concern for disseminated nocardiosis prompted chest CT, which disclosed a 14.5-cm cavitory right upper lobe lesion and bilateral patchy opacities but no lymphadenopathy (Figure 3). MRI of the brain demonstrated multiple ring-enhancing lesions (Figure 4).

Multiple cultures of synovial fluid and sputum showed beaded, branching, gram-positive rods. Blood cultures had no growth, and echocardiography did not show any valvular vegetations. Because the patient had not been on antineoplastic therapy for several months, the absence of tumor burden and lymphadenopathy led us to question the prior presumptive diagnosis of metastatic lung squamous cell cancer.

A CT-guided lung biopsy was planned. However, on hospital day 10, the patient developed progressive hyponatremia and hyperkalemia with seizures and hypotension, so he required antiepileptic therapy and vasopressor support. Because the patient's condition worsened, his

antibiotics were switched to linezolid and meropenem from trimethoprim/sulfamethoxazole and meropenem before the susceptibility report came back. Despite intensive care, he died on hospital day 17 following aspiration and recurrent seizures.

An autopsy showed no evidence of lung carcinoma. Histology of the right upper lobe lesion demonstrated an abscess with granulation tissue and filamentous bacteria, which stained positive with Grocott's methenamine silver. The bacteria were confirmed to be *N. niwae* by culture and 16S rRNA sequencing.

Nocardia species are ubiquitous, soil-borne saprophytes that cause opportunistic infection in hosts with and without underlying immunodeficiency. Case series data suggest that most episodes are a result of hematogenous dissemination from a pulmonary infection.² However, pulmonary nocardiosis is frequently misdiagnosed—occasionally with catastrophic results.

Identification often requires invasive sampling via bronchoscopy with biopsy, but microbiological confirmation is delayed by slow growth on culture and increasing reliance on gene sequencing data from reference laboratories. Signs and symptoms of nocardiosis can suggest other infectious syndromes, as well as noninfectious disorders. Prior case reports note that infection with *Nocardia* species has mimicked malignancy, sarcoidosis, and fungal/mycobacterial infection with misdiagnosis avoided by tissue sampling.^{3,4}

Although the presence of disseminated nocardiosis—and the complete absence of carcinoma—was confirmed on autopsy, the question of whether *N. niwae* infection was misdiagnosed as metastatic lung squamous cell cancer cannot be definitively answered because lung tissue sampling was not carried out at the time of initial diagnosis. It is possible that lung squamous cell cancer was present and responded to the short course of pembrolizumab therapy; complete responses have been reported, albeit rarely. *Nocardia* species pulmonary infection, which can have a chronic, indolent course over a period of many months, as it did in our patient, could have occurred in the setting of immunosuppression, subsequently disseminating while remaining undiagnosed.⁵

MANAGEMENT

The choice of antibiotic for infection caused by *Nocardia* species depends on the susceptibility, severity, and distribution of the disease, as well as the immune status of the patient. Generally, isolated disease that is not severe can be treated with oral trimethoprim/sulfamethoxazole monotherapy, whereas critical disseminated disease requires susceptibility testing and intravenous trimethoprim/sulfamethoxazole with 1 or more additional intravenous agents—imipenem or amikacin, for example. Other options include linezolid and ceftriaxone.

In life-threatening disease, 3 intravenous drugs should be used before susceptibility testing. Our patient was immunocompromised with multiorgan involvement. Therefore, the initial plan was close inpatient monitoring with 6 weeks of intravenous therapy consisting of trimethoprim/sulfamethoxazole, 15 mg/kg, and meropenem, 500 mg, every 4 hours. Alternative agents were to be considered once susceptibility results were available. The in-

patient regimen was to be followed by outpatient therapy with oral trimethoprim/sulfamethoxazole, 10 mg/kg, for 1 year or more.

However, the patient's course was complicated by hyponatremia and hyperkalemia, which are known to be associated with trimethoprim/sulfamethoxazole use in older adults, especially those on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. After he developed the electrolyte imbalances, his regimen was changed to linezolid, 600 mg every 12 hours, and meropenem, 500 mg every 4 hours.

Positive outcomes in nocardiosis are frequently achieved with immediate appropriate treatment and prolonged maintenance therapy. One study of 35 organ transplant recipients demonstrated an 89% cure rate with a prompt and proper regimen.⁶ After hospital discharge, all patients should be seen monthly to monitor their response to therapy, and radiography should be used to evaluate regression of pulmonary and intracranial lesions. Patients with intracranial lesions unresponsive to therapy should be referred to neurosurgical specialists.

Misdiagnosis of nocardiosis and resultant mismanagement can have severe ramifications. Tissue confirmation is critical if these scenarios are to be avoided. In our patient's case, we submit that *N. niwae* caused the initial lung lesion—or cohabitated with a possible malignancy—and then spread systemically following exposure to steroids and chemotherapy. Providers should be cognizant of the challenges inherent in detecting pulmonary and disseminated nocardiosis.

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References

1. Moser BD, Klenk HP, Schumann P, et al. *Nocardia niwae* sp. nov., isolated from human pulmonary sources. *Int J Syst Evol Microbiol* 2011;61(Pt 2):438–442. [PubMed: 20348315]
2. Chaussade H, Lebeaux D, Gras G, et al. *Nocardia* arthritis: 3 cases and literature review. *Medicine (Baltimore)* 2015;94:e1671. [PubMed: 26496274]
3. Abdel-Rahman N, Izhakian S, Wasser WG, Fruchter O, Kramer MR. Endobronchial enigma: a clinically rare presentation of *Nocardia beijingensis* in an immunocompetent patient. *Case Rep Pulmonol* 2015;2015:970548. [PubMed: 26819795]
4. Zuk J, Bazan-Socha S, Zarychta J, et al. Disseminated nocardiosis mimicking exacerbation of pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2013;30:65–69. [PubMed: 24003537]
5. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540–1550. [PubMed: 26712084]
6. Peleg AY, Husain S, Qureshi ZA, et al. Risk factors, clinical characteristics, and outcome of *Nocardia* infection in organ transplant recipients: a matched case-control study. *Clin Infect Dis* 2007;44:1307–1314. [PubMed: 17443467]

Figure 1.

This indurated scaly plaque, measuring 6×3 cm, was in the patient's right pectoral region, superior to the site where a core biopsy had been performed. The specimen from that previous procedure revealed evidence of squamous cell carcinoma.

Figure 2.

Synovial fluid was aspirated from the patient's right elbow. (A) *Nocardia niwae* was identified on a Gram stain (left). (B) Modified acid-fast stain (middle). The specimen was immersed in oil and magnified to 1000 $\times$. (C) A sample was grown on a chocolate agar plate (right).

Figure 3.
Coronal (left) and transverse (right) views of chest computed tomography with intravenous contrast revealed a cavitary mass.

Figure 4. Coronal (left) and transverse (right) views of brain magnetic resonance imaging with gadolinium demonstrated a rim-enhancing lesion.