Clinical Pathologic Conference

An Independent Elderly Woman With Rapid Onset of Coma

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A 75-year-old woman was transferred from a local hospital because of rapid progression to coma preceded by lower back pain and recurrent falls. Cerebrospinal fluid analysis at the local hospital revealed increased protein with a slightly elevated white blood cell count. Our imaging studies revealed multiple punctate foci with nodular enhancement in the brain and multifocal cystic lesions on the chest and abdomen. The patient was empirically treated with antibiotics and corticosteroids without improvement. She died 3 days after transfer, and an autopsy was performed. The differential diagnosis, pathologic findings, and final diagnosis are discussed.

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Report of a Case

A 75-year-old white woman with increasing lower back pain of 2 months' duration was diagnosed as having lumbar spinal stenosis and a vertebral compression fracture. She was treated with epidural corticosteroid injections but continued to experience back pain, impaired mobility, and falls. She was admitted to a rehabilitation facility for physical therapy but developed altered mental status. She was transferred to a local hospital and treated for a urinary tract infection and pneumonia. Her antibiotic regimen (meropenem, vancomycin hydrochloride, and acyclovir) was escalated to empirically treat multidrug-resistant pneumonia and meningitis. She was also treated with 4 mg of dexamethasone every 6 hours. Despite these measures, she quickly became comatose during the 10-day hospital admission and was transferred to our tertiary care hospital for further treatment.

The patient had a medical history of hypertension, hyperlipidemia, anxiety disorder, and gastroesophageal reflux disease. She lived independently, followed up regularly with her primary care physician, and participated in routine health screenings. She had no significant family history, recent travel, or allergies. In addition, she did not use tobacco, alcohol, or illicit drugs.

On admission, she was afebrile and unresponsive to verbal stimuli. Nuchal rigidity was present. Her pupils were equal and sluggishly reactive to light, and her eyes were tonically deviated to the right. Oculocephalic reflex was absent. Corneal reflex was weakly present bilaterally, gag reflex was intact, and nasolabial folds were symmetric at rest. She had weak withdrawal to noxious stimuli in all 4 extremities. Deep tendon reflexes were graded as 0, 1+, 2+, 3+, and 4+ in the upper extremities and trace in the lower extremities, with upgoing plantar reflexes bilaterally.

She was admitted to the neurointensive care unit and intubated for airway protection. Her peripherally inserted central catheter (PICC) was removed and cultured. Acyclovir and vancomycin treatment was continued, and cefepime hydrochloride, doxycycline, and hydrocortisone were added to her treatment regimen. On the basis of the patient's imaging findings, poor clinical prognosis, and advanced directives, her family elected to provide comfort measures only. Neither lumbar puncture nor bronchoscopy with biopsy was performed. The patient died 3 days later.

Laboratory and Imaging Studies

At the local hospital, her laboratory studies revealed an elevated white blood cell (WBC) count of 12,300/µL (to convert to ×10⁹/L, multiply by 0.001) with 31% bands. The result of a nasal swab was positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Blood culture yielded gram-positive bacilli, but the results of subsequent cultures were negative. Sputum cultures yielded *S aureus* (moderate growth) and gram-negative bacilli (light growth), but the results of subsequent cultures were positive for *Pseudomonas aeruginosa* and MRSA. Urine culture yielded *Candida albicans*, but the results of subsequent cultures were negative. Cerebrospinal fluid (CSF) analysis revealed a red blood cell count of 1176/µL, a WBC count of 8/µL (95% neutrophils and 5% lymphocytes), a glucose level of 107 mg/dL (to convert to millimoles per liter, multiply by 0.0185), and a protein level of 0.11 g/dL (to convert to grams per liter, multiply by 10). The results of CSF culture and fungal stain were negative.

After admission to our hospital, her laboratory studies revealed a normal WBC count with predominant neutrophils (neutrophils, 95%), mild anemia with hemoglobin levels of 8.9 to 9.7 g/dL (to convert to grams per liter, multiply by 10), and slightly low platelet counts that ranged from 100 to 110 × 10⁹/L (to convert to millimoles per liter, multiply by 1). She had an erythrocyte sedimentation rate of 84 mm/h and a C-reactive protein level of 149 mg/L (to convert to nanomoles per liter, multiply by 9.524). Her renal and liver function test results, coagulation study results, and cardiac enzyme, folate, cyanocobalamin, and ammonia levels were normal. Her thyrotropin level was within the reference range, but her total triiodothyronine and free thyroxine levels were mildly low. Lyme IgM and IgG, thyroid antibody panel, rapid plasma reagin, and human immunodeficiency virus test results were negative. Serum protein electrophoresis revealed hypogammaglobulinemia, but a small amount of monoclonal IgGκ was detected with a monoclonal spike at 0.2 g/dL. Urine pro-
tein electrophoresis detected free κ and λ light chains, but the concentrations were too low to be quantified. The result of a PICC culture was positive for *Nocardia farcinica* in an aerobic bottle (no growth in an anaerobic bottle). Urine culture revealed 10,000 to 100,000 colonies/mL of coagulase-negative staphylococci. Sputum culture from the endotracheal tube yielded much MRSA and rare *C. albicans*.

Electroencephalography results were abnormal because of moderate diffuse slowing of background activity but no epileptiform discharges. Brain magnetic resonance imaging (MRI) revealed multiple punctate foci of nodular enhancement within the cerebellum and leptomeninges in the posterior fossa (Figure 1, A-C). There was also an abnormal increase in T2 and fluid-attenuated inversion recovery signal in the pons that extended into the medulla (Figure 1, D and E).

Magnetic resonance images of the brain with contrast reveal multiple punctate foci of nodular enhancement within the cerebellum (A-C, yellow arrowheads) and leptomeninges in the posterior fossa (C, blue arrowhead), brainstem (D and E, arrowheads), and left occipital lobe (F, arrowheads). Computed tomogram of the chest with contrast reveals mediastinal lymphadenopathy, pleural effusion, and cavitory nodular opacities in the right lower lung (G, arrowheads). Computed tomogram of the abdomen with contrast reveals a cystic lesion on the left kidney (H, arrowhead).
D and E), the pulvinar of the thalami, the subarachnoid spaces throughout the posterior fossa and bilateral occipital (Figure 1F), and the anterior temporal lobes. Total spine MRI with contrast also revealed compression fractures of the T12 vertebral body with an ill-defined area of enhancement at the posterior vertebral body. Computed tomography of the chest, abdomen, and pelvis revealed mediastinal lymphadenopathy, lobulated right pleural effusion, nodular opacities in the right lower lung (Figure 1G), T12 vertebral body fracture, and cystic lesions of the pancreas and bilateral kidneys (Figure 1H).

Clinical Discussion (Dr Malaty)

The prominent features of this case are rapidly progressive neurologic deterioration and multiorgan involvement, including the brain, lung, vertebrae, kidney, and pancreas. Severe sudden alteration in the level of consciousness in this patient is most likely attributable to a diffuse brain insult. There are multiple brain lesions, including involvement of the brainstem structures (Figure 1, D and E) and bilateral thalami. The differential diagnosis of such a disseminated disease is broad, including neoplastic, infectious, inflammatory, and autoimmune conditions and toxic-metabolic causes.

Given the advanced age of the patient and multifocal enhancing lesions in the brain, a tumor metastatic to the brain should be strongly considered. Most brain metastases originate from cancer of the lung, breast, or melanoma, but renal cell, colon, and gynecologic malignant tumors also make up a significant fraction. Approximately 80% of brain metastases occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem.1

Primary lung cancer is the leading cause of cancer-related death in the United States and worldwide, with brain and bone being the primary sites of metastasis. This patient presented with mediastinal lymphadenopathy, lung nodules, pleural effusion, vertebral body fracture, and multiple brain-enhancing lesions. Consequently, metastatic lung cancer must be considered. She had no pulmonary symptoms or smoking history, but approximately one-third of patients with lung cancer present with symptoms that result from distant metastases. Establishing the diagnosis of metastatic lung cancer requires tissue biopsy, which was deferred in this patient because of a palliative care plan.

Although this patient had lesions in the kidneys and pancreas, primary renal cancer is unlikely given the bilateral involvement of kidneys, and pancreatic cancer rarely metastasizes to the brain or bone. Another possibility is multiple myeloma, considering the back pain with vertebral body fracture, anemia, and abnormal serum protein electrophoresis and urine protein electrophoresis results, although the monoclonal spike level was still low. However, it would be difficult to explain the brain, kidney, and pancreatic lesions solely by multiple myeloma. A bone marrow biopsy would investigate multiple myeloma or other monoclonal gammopathies.

With nuchal rigidity, elevated WBC counts, bandemia, elevated erythrocyte sedimentation rate and C-reactive protein level, positive bacterial culture results, and widespread multiorgan lesions, disseminated infection is a clear consideration. Specifically, disseminated Mycobacterium tuberculosis is a concern because of features of lung nodules, mediastinal lymphadenopathy, back pain with vertebral body fracture (Pott disease), and miliary lesions in the posterior fossa. Similarly, many systemic fungal infections, such as aspergillosis, blastomycosis, histoplasmosis, coccidiomycosis, and mucormycosis, also affect the lung, brain, kidney, bone, skin, and other organs. Both M tuberculosis and fungal infections may present with severe headache, cranial nerve palsy, and signs of increased intracranial pressure; CSF analysis typically reveals a lymphocytic pleocytosis (lymphocyte count up to 1000/μL [to convert to ×10⁹/L, multiply by 0.001]), an elevated protein level (0.1-0.8 g/dL), and a decreased glucose concentration. The classic neuroimaging pattern includes basal cistern meningeval enhancement, posterior fossa cerebral abscesses, and hydrocephalus.2,3 This patient had enhancing parenchymal and meningeval lesions within the posterior circulation but no clear history of exposure to M tuberculosis or fungus. Neither headache nor cranial nerve palsy was initially present, and initial CSF results were not supportive of the diagnosis. Definite diagnosis of central nervous system (CNS) M tuberculosis or fungal infection requires isolation of M tuberculosis or a fungus from the CSF or the brain tissue by histologic identification.

Findings of cultures of blood, urine, sputum, and PICC in this patient were inconsistent; multiple bacterial pathogens were isolated, including MRSA, coagulase-negative staphylococci, Pseudomonas aeruginosa, and gram-positive bacilli, including Nocardia farcinica. All these pathogens have the capacity for widespread infection and septic embolism that involve different body systems, more commonly in patients who are immunocompromised. Notably, disseminated nocardiosis usually originates from the lungs and invades other organs through hematogenous spread, most commonly to the CNS.4 The hallmark of CNS nocardiosis is the formation of parenchymal microabscesses that can occur in any region of the brain.4 Routine neuroimaging studies often fail to distinguish between acute pyogenic bacterial abscesses and neoplastic brain lesions. A previous report5 indicated that magnetic resonance spectroscopy in conjunction with routine MRI may readily differentiate multiple abscesses from tumor metastases, offering a future tool for rapid, noninvasive diagnosis. However, truly establishing an infectious origin requires CSF cultures, which were nondiagnostic in this patient; blood cultures, which were inconsistent in our case; or histopathologic examination and tissue culture, which were only performed postmortem.

Sarcoidosis is a relatively common inflammatory disorder that frequently affects the lung and nervous system. Hilar and mediastinal lymphadenopathies are usually present, with or without concomitant parenchymal abnormalities. Granulomatous basilar meningitis or parenchymal inflammation is responsible for most of the CNS manifestations, and their enhancement on neuroimaging suggests active inflammation.6 However, the complete unresponsiveness to corticosteroid treatment in this case makes neurosarcoidosis less likely. The CSF angiotensin-converting enzyme has poor sensitivity7 and was not tested. Bronchoscopy with biopsy to assess for noncaseating granulomas was not pursued.

Some systemic vasculitides, such as granulomatosis with polyangitis (Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), are multisystem autoimmune disorders that affect the upper airway, lung, kidney, skin, and, to a lesser extent, nervous system.8 In our case, these diagnoses are unlikely given the patient’s acute presentation, rapid progression, and lack of characteristic symptoms or responsiveness to corticosteroids. Antineu-
Pathologic Discussion (Dr. Yachnis)

A general autopsy of the patient revealed the following: (1) a middle lobe nodule in the right lung (2.7 cm) with central cavitation filled with viscous green-yellow material; (2) bilateral cystic pulmonary lesions (up to 0.5 cm) filled with viscous green-yellow material; (3) green-yellow adhesive visceral pleural plaques on the right lung (0.2-0.5 cm); (4) bilateral pleural effusion of clear yellow fluid; (5) bilateral renal capsules with granity surfaces covered with punctate foci of green-yellow material; (6) right kidney with a single cystic lesion (0.5 cm) filled with viscous green-yellow material; (7) pancreatic parenchyma with granity green-yellow material; and (8) splenic capsule with focal punctate foci of green-yellow material. The vertebral bodies were not sampled for autopsy.

Gross neuropathologic examination revealed focal hyperemia of the cerebellar hemispheres and a poorly defined softened area in the right lateral cerebellar hemisphere. There were several minute (approximately ≤1 mm), dull, gray-green ovoid lesions within the cerebellar cortex. Serial coronal section of the cerebral hemispheres revealed multifocal, rather well-circumscribed lesions, varying in size from 1 to 4 mm in greatest dimension, that were located throughout the cerebral hemispheres—especially at the gray-white matter junction of the middle frontal, middle, and inferior parietal gyri bilaterally, mammillary bodies, and lateral geniculate nucleus (Figure 2A). Sections of the brainstem had focal hyperemia in the central region of the pons.

Histopathologic examination of multiple levels of the neuraxis revealed numerous multifocal necrotizing microabscesses (Figure 2B) with occasional foci of associated incomplete ischemic necrosis in adjacent parenchyma. Grocott methenamine silver stain confirmed numerous branching filamentous organisms within the microabscesses (Figure 2C). The organisms were also weakly positive on acid-fast stain but negative on tissue Gram stain. These lesions were present within the bilateral frontal lobes, right parietal and temporal lobes, left basal ganglia, left occipital lobe, cerebellum, midbrain, pons, and medulla. The inflammation focally spread to overlying meninges in some areas.

The most significant finding of the autopsy is a widespread disseminated infection with a branching filamentous organism. Foci of infection were observed in most major organ systems. Characterization of the responsible organism by further microbiological study revealed branching filamentous rods that were weakly positive on acid-fast stain, suggesting Nocardia species. This finding correlates with the organisms isolated from the patient’s PICC culture, N farcinica, which was later confirmed by the Florida Department of Health Bureau of Laboratories.

Conclusions

Nocardiosis is an uncommon bacterial infection caused by aerobic actinomycetes in the genus Nocardia. Nocardia species are gram-positive bacilli with delicate filamentous branching rods and weak acid-fast staining. Among the most common Nocardia species associated with human disease, N farcinica appears to be more virulent, causing disseminated disease resistant to antimicrobials.9

Nocardiosis is typically regarded as an opportunistic infection, but approximately one-third of infected patients are immunocompetent.4 Although our patient was presumed to be immunocompetent, it is possible that an occult malignant tumor, such as multiple myo-
eloma, rendered her at higher risk of opportunistic infections. Furthermore, the use of endovascular devices, such as central venous catheters, has been increasingly recognized to be associated with *Nocardia* bacteremia.\(^1\) In the current case, although *N farcinica* was isolated from the PICC, this catheter does not seem to be the source of the infection because the onset of symptoms occurred before PICC insertion. It is unknown whether the patient’s local corticosteroid injection into the lower back was actually the source of infection.

A definitive diagnosis of nocardiosis requires the isolation and identification of the organism from a clinical specimen, often requiring an invasive procedure to obtain an adequate specimen. In addition to nonspecific clinical presentation, delay in diagnosis is often due to the difficulty in culturing *Nocardia* species. In our patient, only one of many blood cultures eventually yielded Nocardia and not until devastating clinical progression had occurred. This finding highlights the challenge in isolating this organism in culture. Polymerase chain reaction for identification of *Nocardia* species is promising, with its high sensitivity and specificity and rapid diagnosis.\(^11,12\) However, it is not currently available in most clinical laboratories.

Antibiotics that are typically effective against Nocardia include the combination of trimethoprim and sulfamethoxazole, amikacin, imipenem, and third-generation cephalosporins. However, antimicrobial susceptibility testing is always necessary to ensure optimal antibiotic therapy. The duration of antimicrobial treatment for severe disease has not been determined, but most recommend a prolonged course because of the relapsing nature of Nocardia infection. Despite progress in clinical diagnosis and treatment, mortality due to pulmonary nocardiosis continues to be high (14%-40%), with a marked increase in CNS dissemination.\(^13\) In a 2007 report\(^14\) of 31 cases of pulmonary nocardiosis, the mortality was 38.7% but increased to 64% in disseminated nocardiosis and 100% with CNS involvement. Other important points that affect the prognosis are the delay in diagnosis and, consequently, the delay in treatment.\(^13\) Thus, clinical suspicion and early recognition are essential to initiate appropriate therapy and reduce mortality.

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**REFERENCES**


