CLINICAL CARE CONUNDRUMS

Overcome by Weakness

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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An 89-year-old man presented to the emergency department with progressive fatigue, confusion, and generalized weakness over 2 months, worsening in the prior few days.

Four categories of disease account for most cases of confusion in the elderly: metabolic derangements; infection (both within and outside of the central nervous system); structural brain disorder (eg, bleed or tumor); and toxins (generally medications). It will be important early on to determine if weakness refers to true loss of motor function, reflecting a neuromuscular lesion.

At baseline, the patient had normal cognition, ambulated without assistance, and was independent in activities of daily living. Over the preceding 2 months, general functional decline, unsteady gait, balance problems, and word-finding difficulty developed. He also needed a front-wheel walker to avoid falling. One month prior to presentation, the patient's children noticed he was markedly fatigued and was requiring a nightly sedative-hypnotic in order to fall asleep.

He denied any recent travel, sick contacts, or recent illness. He denied vertigo, dizziness, or syncope. He reported occasional urinary incontinence which he attributed to being too weak to get to the bathroom promptly.

This rapid progression over 2 months is not consistent with the time course of the more common neurodegenerative causes of dementia, such as Alzheimer's or Parkinson's disease. In Parkinson's, cognitive impairment is a late feature, occurring years after gait and motor disturbances develop. Normal pressure hydrocephalus, which causes the classic triad of incontinence, ataxia, and confusion, would also be unlikely to develop so abruptly. Although we do not think of vascular (multi-infarct) dementia as having such a short time course, on occasion a seemingly rapid presentation is the post-script to a more insidious progression that has been underway

for years. A subdural hematoma, which may have occurred with any of his falls, must also be considered, as should neoplastic and paraneoplastic processes.

His past medical history included paroxysmal atrial fibrillation, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease complicated by prior myocardial infarction for which he underwent coronary artery bypass grafting 7 years prior, mild aortic sclerosis and insufficiency, mild mitral regurgitation, anemia, recurrent low-grade bladder cancer treated with serial local resections over the last 8 years, low-grade prostate cancer which had not required treatment, hypothyroidism, chronic kidney disease, and lumbar spinal stenosis.

His atrial fibrillation and valvular disease put him at risk for thrombotic and infective embolic phenomena causing multiple cerebral infarcts. He has all the requisite underlying conditions for vascular dementia. Untreated hypothyroidism could explain his decline and sedation. Prostate and bladder cancers would be unusual causes of subacute central nervous system (CNS) disease. Finally, his chronic kidney disease may have progressed to uremia.

One year prior to admission, the patient developed bilateral shoulder pain, right-sided headache with loss of vision in his right eye, fevers, and an elevated erythrocyte sedimentation rate (ESR). Although temporal artery biopsy specimens did not reveal arterial inflammation, he was started on high-dose prednisone for polymyalgia rheumatica and giant cell arteritis (GCA); he experienced improvement in his ESR and in all symptoms, with the exception of permanent right eye blindness. Maintenance prednisone was continued for disease suppression.

Even without confirmatory biopsy results, the clinical case for GCA was compelling and the rationale for starting steroids strong; his sustained response over 1 year further supports the diagnosis. GCA is almost always confined to extracranial vessels, and altered sensorium would be an unusual manifestation. His extended treatment with prednisone expands the list of CNS and systemic infections, particularly opportunistic ones, for which he is now at risk.

Outpatient medications were prednisone at doses fluctuating between 10 and 20 mg daily, furosemide 20 mg daily, amiodarone 200 mg daily, levothyroxine 50 mcg daily, alendronate 70 mg weekly, eszopiclone 1 mg nightly, losartan 50 mg daily, and warfarin. The patient was an accomplished professor and had published a book 1 year prior to admission. He quit smoking over 30 years ago, and he occasionally drank wine. He denied any drug use.

Three months prior to the current presentation, the patient was hospitalized for right upper-lobe pneumonia for which he received a course of doxycycline, and his symptoms improved. Follow-up chest x-ray, 4 weeks later (2 months prior to admission), showed only slight improvement of the right upper-lobe opacity.

Leading possibilities for the persistent lung opacity are cancer and untreated infection. After 3 decades of being tobacco-free, his smoking-related risk of cancer is low, but remains above baseline population risk. There are at least 4 ways untreated lung cancer may render patients confused: direct metastases to the brain, carcinomatous or lymphomatous meningitis, paraneoplastic phenomenon (eg, limbic encephalitis), and metabolic derangements (eg, syndrome of inappropriate antidiuretic hormone secretion, hypercalcemia).

The upper-lobe infiltrate that failed to improve with doxycycline could also reflect an aspiration pneumonia that evolved into an abscess, or an infection with mycobacteria or endemic fungi.

In the emergency department, the patient's temperature was 38.5°C, blood pressure 139/56 mmHg, heart rate 92 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation while breathing ambient room air was 98%.

He was alert and well-appearing. Jugular venous pressure was normal. The thyroid was normal. He had rhonchi in his right anterior upper chest and right lower lung base. Cardiac exam demonstrated a regular rhythm, with a 3/6 systolic murmur at the second right intercostal space that radiated to the carotids, and a 2/6 nonradiating holosystolic murmur at the apex. Abdomen was soft with no organomegaly or masses. There was no lymphadenopathy, and his extremities showed no clubbing or edema. There were multiple contusions in various stages of healing on his legs.

He was confused, had word-finding difficulty, and frequently would lose his train of thought, stopping in midsentence. He had no dysarthria. Cranial nerves were normal, except for reduced visual acuity and diminished pupillary response to light in his right pupil, which had been previously documented. Finger-to-nose testing was slow bilaterally, but was more sluggish on the right. Rapid alternating hand movements were intact. He was unable to perform heel-to-shin testing. Sensation was intact. Plantar reflexes were flexor bilaterally. Strength in his limbs was preserved both distally and proximally, and deep tendon reflexes were normal. However, he was unable to sit up or stand on his own due to weakness.

The fever on prednisone is a red flag for infection. The infection may be the primary diagnosis (eg, meningoencephalitis) or may reflect an additional superimposed insult (eg, urinary tract infection) on the underlying encephalopathy. Two murmurs in a febrile patient with the multifocal CNS findings suggest endocarditis. The abnormalities on chest examination could indicate a lung infection complicated by hematogenous spread to the brain, such as a lung abscess (secondary to the aspiration event), tuberculosis (TB), or endemic fungal infection.

Serum chemistries were normal, and the serum creatinine was 1.1 mg/dL. White blood cell count was 20,100 per mm³ with 90% neutrophils, 9% lymphocytes, and 1%
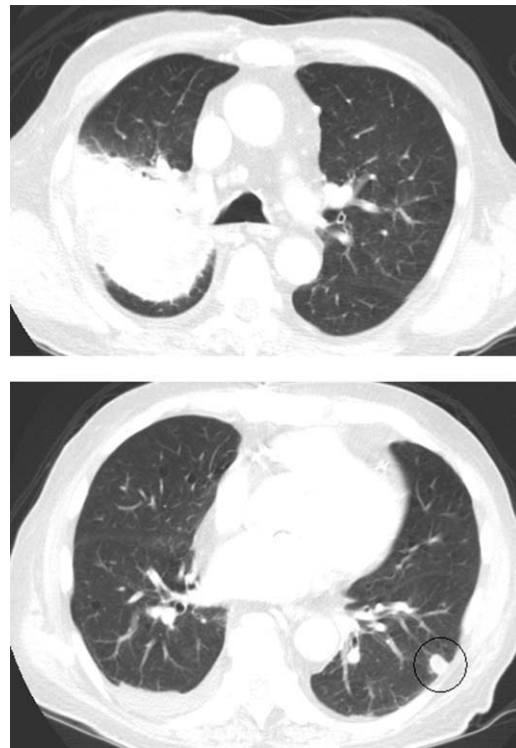

FIG. 1. Computed tomography of the chest. There is opacification of the entire posterior segment of the right upper lobe (A); a 10-mm superior segment left lower-lobe nodule (B; shown in circle), several right lower-lobe nodules and enlarged pretracheal and right hilar lymph nodes, and a small right pleural effusion is present.

monocytes. Hemoglobin was 13.7 g/dL, platelet count was 464,000 per mm³. Thyroid stimulating hormone (TSH) was 6.0 μIU/mL (normal, <5.5). International normalized ratio (INR) was 2.2. Urinalysis was normal. Transaminases, bilirubin, and alkaline phosphatase were normal. Lactate was 1.9 mmol/L.

Electrocardiogram (EKG) was unchanged from his baseline. ESR was >120 mm/hr (the maximum reportable value); his ESR measurements had been gradually rising during the previous 4 months. Chest x-ray demonstrated a right upper-lobe opacity, slightly more pronounced in comparison with chest x-ray 2 months earlier.

His fever, leukocytosis, elevated ESR, and thrombocytosis all reflect severe inflammation. While infection and then malignancy remain the primary considerations, a third category of inflammatory disease—autoimmunity—warrants mention. For instance, Wegener's granulomatosis can cause pulmonary and CNS disease in the elderly.

Intravenous ceftriaxone and oral doxycycline were administered. Chest computed tomography (CT) (Figure 1) demonstrated dense right upper-lobe mass-like consolidation with associated adenopathy and pleural effusion; in addition, several nodules were present in the left and right lower lobes, the largest of which was 10 mm. CT of the chest 10 months prior to current admission had been normal. CT of the brain, performed without contrast, demonstrated multiple areas of abnormal vasogenic edema with suggestion of underlying masses.
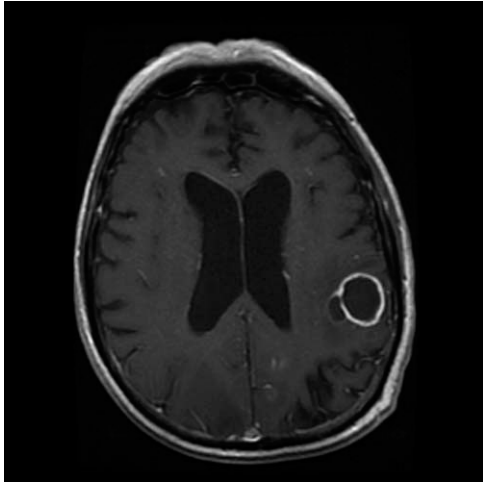
FIG. 2. Magnetic resonance imaging (MRI) of the brain with and without gadolinium. MRI demonstrates multiple supratentorial ring-enhancing lesions lying at the junction of gray and white matter.

The imaging provides evidence of a combined pulmonary–CNS syndrome. It is far more common for disease to originate in the lungs (a common portal of entry and environmental exposure) and spread to the brain than vice versa. The list of diseases and pathogens that affect the lungs and spread to the brain includes: primary lung cancer, lymphoma, bacteria, mycobacteria, fungi, molds (eg, *Aspergillus*), Wegener's granulomatosis, and lymphomatoid granulomatosis. Bacterial lung abscess, such as that caused by *Streptococcus milleri* group, may spread to the brain. *Nocardia*, a ubiquitous soil organism, infects immunocompromised patients and causes a similar pattern. Actinomycosis is an atypical infection that may mimic cancer, particularly in the lungs; while head and neck disease is characteristic, CNS involvement is less so. Overall, the imaging does not specifically pinpoint 1 entity, but infection remains heavily favored over malignancy, with autoimmunity a distant third.

Respiratory cultures showed normal respiratory flora. Blood cultures grew no organisms. Two samples of induced sputum were negative for acid-fast bacilli (AFB) on smear examination. Forty-eight hours after a purified protein derivative (PPD) skin test was placed, there was 0 mm of induration. Magnetic resonance imaging (MRI) of the brain (Figure 2) demonstrated 8 ring-enhancing supratentorial lesions at the gray–white junction.

Negative blood cultures substantially lower the probability of bacterial endocarditis; there are no epidemiologic risk factors for the rare causes of culture-negative endocarditis (eg, farm exposure, homelessness). Two negative smears for AFB with dense pulmonary or cavitary disease signify a low probability of tuberculosis.

In the setting of depressed cell-mediated immunity (eg, human immunodeficiency virus [HIV] infection or chronic prednisone use), multiple ring-enhancing CNS lesions are a classic appearance of toxoplasmosis, but they also are typical of bacterial brain abscesses and *Nocardia*. Brain metastases are usually solid, but as central necrosis develops, peripheral enhancement may appear. The diffuse distribution and the localization at the gray–white junction further support a hematogenously disseminated process, but do not differentiate infection from metastases.

Transthoracic echocardiogram demonstrated normal left ventricular ejection fraction, clinically insignificant aortic sclerosis and mitral regurgitation, and no evidence of vegetations. Results of a CT-guided fine-needle aspiration of the lung were nondiagnostic, showing necropurulent material and benign lung parenchyma with fibrosis. A core biopsy of the lung showed alveolar tissue with patchy mild deposition of fibrinous material and rare scattered acute and chronic inflammatory cells without granulomas. Pleural fluid cytology showed reactive mesothelial cells with mixed inflammatory cells. There were no fungal elements or malignant cells.

The failure to detect malignancy after 2 biopsies and 1 thoracentesis lowers the suspicion of cancer, and thereby bolsters the probability of atypical infections which may elude diagnosis on routine cultures and biopsy. A detailed history, with attention to geographic exposures, is warranted to see which endemic mycosis would put him most at risk. Based on his California residency, disseminated coccidiomycosis or the ubiquitous *Cryptococcus* are conceivable. *Nocardia* remains a strong consideration because of his chronic immunosuppression and the lung-CNS pattern.

Fungal stains and cultures from the biopsies and pleural fluid were negative. Serum antibodies to coccidiomycosis and serum cryptococcal antigen tests were negative. On the eighth hospital day, the microbiology lab reported a few acid-fast bacilli from a third induced sputum sample. RNA amplification testing for *Mycobacterium tuberculosis* was negative. Due to his continued decline, the patient met with the palliative care team and expressed his desire to go home with hospice. While arrangements were being made, he died later that day in the hospital.

There is reasonable evidence that tuberculosis is not the culprit pathogen here: negative PPD, 2 negative sputa in the setting of a massive necrotic lesion, and a negative RNA amplification test. Nontuberculous mycobacteria such as *Mycobacterium avium* complex (MAC) and *M. kansasii* may cause disease similar to TB, but they are usually not this difficult to identify. *Nocardia* is classically a weakly acid-fast positive bacteria and fits this patient's clinical picture best.

Four colonies of *Nocardia* (not further speciated) were identified postmortem from the patient's sputum.

DISCUSSION

Nocardia species are ubiquitous soil-dwelling, Gram-positive, branching rods which are weakly positive with acid-fast staining.[1] Almost all *Nocardia* infections occur in patients with immune systems compromised by chronic disease (HIV, malignancy, alcoholism, chronic lung or kidney disease) or by medications. Corticosteroid treatment is the most frequent risk factor. In cases of nocardiosis in patients taking steroids, the median daily prednisone dose was 25 mg (range, 10–80 mg) for a median duration of 3 months.[2,3]

Nocardia should be considered in any patient with unexplained pulmonary, CNS, or cutaneous disease and appropriate risk factors. Pulmonary disease is most common, seen in approximately two-thirds of patients, and is typically bilateral. Chest radiographic findings include infiltrates (59%), nodules (35%), effusions, and cavities.[2] Up to half of all cases of pulmonary nocardiosis are associated with hematogenous dissemination, most commonly to the CNS, where manifestations include incidentally discovered asymptomatic lesions,

headache, confusion, and focal neurologic deficits; meningitis is rare.[1] CNS involvement and severe predisposing illness are adverse prognostic markers.

Diagnosis of nocardiosis is typically delayed by 6 weeks to 1 year.[4,5] This has been attributed to its rarity, its nonspecific and indolent presentation, its slow growth, and the difficulty isolating *Nocardia* from clinical specimens. Although *Nocardia* may disseminate widely to almost any site, isolation of *Nocardia* from blood cultures is rare. Clinicians must rely on sputum or tissue samples to demonstrate the characteristic Gram-positive rods which stain weakly on acid-fast preparations. Polymerase chain reaction (PCR)-based tests improve the yield but are not routinely available.

The standard antibiotic for the treatment of *Nocardia* infections is trimethoprim-sulfamethoxazole (TMP-SMX) which has excellent CNS penetration. In patients with pulmonary disease or CNS dissemination, a second parenteral antimicrobial (usually amikacin or imipenem) is typically added to TMP-SMX, and treatment is extended to 12 months or longer.[6,7] Prophylaxis with TMP-SMX, which is usually prescribed to prevent *Pneumocystis jirovecii* in susceptible hosts, also reduces the incidence of *Nocardia*.[2,3,6] *Nocardia*'s restricted susceptibility pattern presents a challenge for hospitalists, as TMP-SMX and aminoglycosides are rarely administered empirically for cases of suspected pneumonia or atypical pulmonary infections (other than *P. jirovecii*).

When confronted with the pattern of simultaneous pulmonary and CNS lesions, hospitalists must consider infections (lung abscess, mycobacteria, fungi, *Nocardia*), malignancies, and autoimmune conditions (sarcoidosis, Wegener's granulomatosis). This patient's weakness was a direct result of his weakened immune system, which allowed this weakly acid-fast organism to flourish. Only by recognizing the possibility of nocardiosis (eg, a patient receiving steroids who develops pulmonary and CNS lesions) is there hope for early diagnosis and treatment.

TEACHING POINTS

1. Suspect disseminated nocardiosis in immunocompromised patients with unexplained pulmonary disease and CNS disease characterized by multiple ring-enhancing abscesses.
2. Corticosteroid treatment is the most common risk factor for *Nocardia* infections. Patients taking prednisone at doses in excess of 10 mg daily for greater than 3 months should receive *P. jirovecii* prophylaxis with TMP-SMX, which also reduces the incidence of *Nocardia*.
3. Prolonged courses of TMP-SMX combined with at least 1 other agent for at least 6–12 months are typically required to treat disseminated *Nocardia*.

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