CLINICAL VIGNETTE

Legionnaires' Disease Presenting as Encephalopathy in a Returning Traveler: A Diagnostic Dilemma

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Case Presentation

A 75-year-old female with a history of recurrent aseptic meningitis, psoriatic arthritis, and chronic migraines was brought to the hospital by family for altered mental status.

One month prior to admission, the patient went on a three-week cruise in southeast Asia with family members, traveling to Thailand, Indonesia, Hong Kong, and Vietnam. When not aboard the ship, the patient and family stayed at hotels. Soon after arrival home, she was involved in a minor motor vehicle accident rear-ending another vehicle. The following morning, she awoke with dizziness, poor balance, and difficulty speaking, which prompted family to bring the patient to the hospital.

Her family reported that the patient is followed by a neurologist after multiple episodes of aseptic meningitis. She is prescribed acyclovir for prophylaxis. She also takes tofacitinib for psoriatic arthritis. The family reports the patient has a slow progressive decline in cognition over three months. She now had more difficulty paying bills and performing other instrumental activities of daily living (iADLs).

On evaluation, the patient reported a cough but was unsure when it developed. She denied headache, nausea, vomiting, dysuria, rash, and diarrhea. Vital signs included normal temperature, blood pressure 141/83, HR 114, normal respiratory rate with 94% saturation on ambient air. She had word finding difficulty and was oriented only to self. There was no focal neurologic deficits. Laboratory values were notable for white blood count of 9.4, platelet count of 114, and mild transaminase elevation (AST 227, ALT 84). Total creatine kinase was elevated to 4,018. Urinalysis showed 3+ blood on dipstick with 10 RBCs per high power field. She underwent computed tomography (CT) of the brain with contrast which did not show evidence of acute hemorrhage or infarction. CT of the abdomen and pelvis did not show any acute abnormalities. Chest CT angiogram showed multiple lobar pulmonary emboli as well as ground glass and consolidative opacities in right lower and left upper lobes concerning for lung contusion versus aspiration. She was started on intravenous heparin. Echocardiogram showed normal ejection fraction and no evidence of pericardial effusion or right heart strain.

On hospital day 1, the developed fever to 103.4F and was initiated on empiric antibiotics for meningitis (vancomycin, ceftriaxone, acyclovir and ampicillin). Lumbar puncture, and cerebrospinal fluid (CSF) analysis showed a normal opening pressure, one nucleated cell, and normal glucose and protein levels. her antibiotics were transitioned to ceftriaxone monotherapy for presumed aspiration pneumonia. Her hospital stay was notable for recurrent daily fevers, waxing and waning alertness with poor attention span and intermittent incoherent speech. Blood and urine cultures were negative as were two blood parasite panels. A brain MRI/MRA showed a small cytotoxic focus in the splenium of the corpus callosum. The patient's fevers and encephalopathy persisted for several days, and labs revealed progressively worsening anemia and thrombocytopenia. The patient continued to have worsening productive cough without other infectious symptoms. She developed worsening hypoxia and required 2 to 4 liters of supplemental oxygen.

By hospital day 5, the patient's fevers began to improve, and her anemia, thrombocytopenia, transaminases and creatine kinase levels showed improvement. At this time, a Karius test from admission returned showing Legionella and Pseudomonas. Subsequent urine Legionella antigen test also resulted positive, and the patient was started on 2-week course of levofloxacin. Her mentation continued to improve, and she was discharged to a rehab facility. Her case was reported to the department of health. At infectious disease follow-up, she noted feeling stronger with improvement in exertional dyspnea and denied fever and cough.

Discussion

Legionella pneumophilia most commonly causes pneumonia known as Legionnaires' disease. Extrapulmonary disease is rare but can include cellulitis, septic arthritis, meningitis and endocarditis. Outbreaks are often associated with contaminated water supplies to large facilities such as hotels. Symptom onset is typically 1 to 14 days from exposure. Legionnaires' disease presents similarly to other forms of pneumonia with fever, cough, and dyspnea. Radiographic findings are similar to more common forms of pneumonia and often show a patchy unilobar infiltrate or consolidation. Additional clinical features that may alert the physician to Legionnaires' disease include gastro-

intestinal symptoms such as diarrhea, hyponatremia (due to the syndrome of inappropriate antidiuretic hormone), and elevated liver function tests. Immunocompromised patients are at increased risk of acquiring infection and poorer outcomes.[1]

Diagnosis can be made through PCR testing of expectorated sputum which can detect all relevant serotypes. When not available or in patients without sputum production (as in our patient), urine antigen testing is an alternative option for diagnosis. Urine assays only detect *Legionella pneumophilia* serogroup 1, which is the most prevalent variant leading to infection (accounting for 80 to 90% of US cases).[2] The assay sensitivity is 70 to 80 percent with excellent specificity.[3] Culture is still considered the gold standard of diagnosis but can be technically challenging to perform.

Either levofloxacin or azithromycin can be used to treat Legionnaires' disease. The optimal duration of therapy is uncertain and dependent on patient risk factors and clinical course. A short course (3 to 7 days) may be appropriate in mild disease, while a longer course (10 to 14 days or longer) is reserved for patients who are immunocompromised, have complications such as extrapulmonary disease, or have persistent symptoms.[4]

Our patient's clinical presentation had several features consistent with Legionella pneumonia. She was immunocompromised due to tofacitinib therapy with recent travel on a cruise ship and hotel stays increased exposure risk. Lab abnormalities included transaminase elevation (commonly seen) and rhabdomyolysis, which has been described in several case reports.[5] In addition, small cytotoxic focus in the splenium of the corpus callosum on brain MRI is nonspecific and can be seen in variety of metabolic, iatrogenic, or infectious etiologies, but has been previously described in a patient with Legionnaires' disease.[6]

The patient represented a diagnostic challenge for several reasons. She presented with progressive encephalopathy on the background of subacute to chronic cognitive decline for many months with a history of recurrent CNS infection. It was initially unclear whether her presentation represented a progression of a chronic unifying diagnosis, or an acute process superimposed on a background of a progressive neurologic disease like dementia. The presence of fever raised suspicion for an acute infectious process, especially in light of her recent travel history. The findings of pulmonary embolism and aspiration on chest imaging provided plausible alternate explanations for the patient's febrile illness. Her unremitting fevers despite broad antibiotics and initial negative testing (including blood and urine cultures, imaging of the abdomen, and negative CSF analysis) supported this theory. Eventually return of a Karius test led to diagnosis of Legionella pneumonia. The Pseudomonas cultures was not felt to be clinically relevant, and should been sensitive to levofloxacin. It is important to consider Legionnaires' disease in any patient admitted for community acquired pneumonia, especially in patients who are immunocompromised, with recent travel history, with additional gastrointestinal symptoms, or who present in the setting of known outbreaks. Urine legionella antigen test performed earlier would have led to earlier diagnosis. Fortunately, our patient responded well to treatment and had a good outcome.

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