A 74-year-old man was brought to the emergency department after being found confused and incapacitated at home. The patient lived in a residential hotel and had previously been healthy and socially active. Having not seen him for three days, his friends entered his room and found him on the floor, covered in stool. The patient was conversant but confused, recalling only a recent fall and his inability to get up.

Causes of acute alteration in mental status fall primarily into four categories: infectious, neurologic, drug-related, and metabolic. In elderly patients, infections are the most common cause, although the other causes remain frequent enough to be pursued just as assiduously. Neurologic causes include hemorrhagic and nonhemorrhagic stroke, seizures, and subdural hematoma. Medications such as sedatives and opiates commonly cause confusion. Metabolic disturbances include alcohol withdrawal, sodium disorders, hyperosmolar coma, and uremia. Other conditions, such as acute myocardial infarction or an intraabdominal infection, can develop atypically in the elderly, predominantly with confusion as the main finding.

The patient’s conversation was tangential. He reported fatigue, diffuse weakness, and a minimally productive cough of four days’ duration. He reported that he had no previous medical problems and had not sought medical care for many years; that he took no regular medications; and that he had not traveled outside the United States in more than 30 years. He had quit smoking 15 years earlier and reported no serious alcohol or illicit-drug use.

Pneumonia is now my leading diagnosis. Elements of the clinical assessment do not indicate which type of pneumonia, although Streptococcus pneumoniae is probably the leading cause of severe community-acquired pneumonia. Pneumococcal pneumonia could certainly account for the patient’s confusion, even without overt bacteremia. Lung cancer presenting as postobstructive pneumonia is possible, given his smoking history, as is cancer-induced hypercalcemia. An acute exacerbation of chronic bronchitis is unlikely to present in this manner.

On physical examination, the patient was disheveled but in no acute distress. He was afebrile with a heart rate of 103, a respiratory rate of 16 breaths per minute, a blood pressure of 145/72 mm Hg, and an oxygen saturation of 95 percent breathing room air. He had mildly icteric sclera and several missing front teeth; the remainder of the examination of his head was normal. His neck was supple without evidence of meningeal irritation. He had occasional inspiratory crackles in the lower left lung field, and the cardiac examination revealed a 2/6 early systolic murmur at the lower left sternal border that did not change with inspiration. His abdomen was soft without tenderness or hepatosplenomegaly. Bowel sounds were present. The rectal examination revealed...
The patient's vital signs and lung findings are consistent with the presence of pneumonia, but the icterus adds additional possibilities. Though the patient reported that he did not drink heavily, his appearance obliges us to consider the possibility of alcoholic liver disease, complicated by pneumonia and hepatic encephalopathy. We should also consider other causes of jaundice. Acute viral hepatitis seems unlikely without recent exposure risks. Cholecystitis or gallstone pancreatitis could cause icterus, but he reported no abdominal pain. Hemolytic causes of jaundice, including unrecognized chronic lymphocytic leukemia, should be considered. Given the presence of a heart murmur, endocarditis is possible. Nevertheless, community-acquired pneumonia remains the most likely diagnosis.

Laboratory tests revealed a white-cell count of 8300 per cubic millimeter, a hematocrit of 43 percent with a mean corpuscular volume of 89.5 µm³, and a platelet count of 69,000 per cubic millimeter. The serum sodium concentration was 132 mmol per liter, and the serum calcium concentration was 8.1 mg per deciliter (2.0 mmol per liter); other serum electrolyte levels were normal. The results of other laboratory tests were as follows: blood urea nitrogen, 31 mg per deciliter (11.1 mmol per liter); aspartate aminotransferase, 256 U per liter; alanine aminotransferase, 77 U per liter; alkaline phosphatase, 214 U per liter; total bilirubin, 6.2 mg per deciliter (106.0 µmol per liter); direct bilirubin, 3.5 mg per deciliter (59.8 µmol per liter); and creatine kinase, 26 U per liter. His albumin level was 1.9 g per deciliter, and the prothrombin time was 13.4 seconds (international normalized ratio, 1.2). The partial-thromboplastin time was elevated, at 37.9 seconds. Other than revealing tachycardia, his electrocardiogram was normal. A chest radiograph obtained with portable equipment revealed slight haziness in the left lower lobe with clearly visible borders of the left heart and diaphragm — findings that are most consistent with the presence of atelectasis. Radiographs of his hips and lower extremities revealed no fractures. Two sets of blood cultures were performed.

Despite the patient’s denial of excessive alcohol use, it is increasingly difficult to discount the possibility of cirrhosis. The levels of aspartate aminotransferase and alanine aminotransferase in combination with thrombocytopenia (not to mention the several missing teeth) all suggest the possibility of alcoholic cirrhosis. Acute causes of liver injury seem less likely, as they would leave unexplained the low albumin level, and the history was not consistent with chronic malnutrition. Given the hyperbilirubinemia, I would also consider cholestatic processes, especially cancer of the gallbladder or pancreas. Intrahepatic causes of cholestasis are possible, including infiltrative disorders (e.g., sarcoidosis or amyloidosis), infections (e.g., abscess or tuberculosis), and metastatic carcinoma.

Regardless of the underlying problem, an acute event has also occurred. Given the patient’s age, the absence of fever does not diminish my concern about infection; this remains the most likely cause. Although the findings on the chest radiograph appear to be consistent with atelectasis, pneumonia is a reasonable diagnosis. At this point, I would err on the side of administering empirical antibiotics to provide coverage for common bacterial causes of pneumonia and for an abdominal infection such as cholangitis. I would obtain a measurement of the serum ammonia level to see whether hepatic encephalopathy may account for the patient’s delirium.

The patient was admitted with a diagnosis of dehyd...
32 mm Hg, and a pH of 7.38 while the patient was breathing 6 liters of oxygen through a nasal cannula. A computed tomographic (CT) scan of the head, obtained without the administration of contrast material, was normal except for the finding of multiple small old infarcts that were consistent with hypertensive disease. Blood cultures showed no growth of any organisms. Intravenous fluids were stopped, and the patient was given intravenous furosemide for presumed pulmonary edema. His mental status worsened.

Although empirical treatment for pneumonia was reasonable, the possible hepatobiliary problem seems to have been largely ignored. Abdominal imaging to evaluate the liver, biliary tract, portal vein, and pancreas remains important. What about the lungs? Lack of improvement for 24 to 48 hours is possible with uncomplicated community-acquired pneumonia, but improvement followed by worsening is a reason for concern. One possibility is that though he has pneumonia, the organism is resistant to the antibiotics administered. Another possibility is that the primary problem is delirium and that he has aspirated and now has chemical pneumonitis or a new pneumonia. Finally, one must consider the possibility that the patient mistakenly did not receive his antibiotics.

Instead of pneumonia, the patient may have cardiogenic or noncardiogenic pulmonary edema. Given his murmur, it is possible that he has valvular heart disease or alcoholic cardiomyopathy. Right-sided endocarditis with septic emboli to the lungs is unlikely unless he uses injection drugs. Also, the murmur’s characteristics are not suggestive of tricuspid regurgitation, and the negative blood cultures to date are reassuring. The patchy infiltrates on his chest radiograph may represent acute respiratory distress syndrome due to worsening sepsis rather than pneumonia. The cause of the sepsis may be an intraabdominal infection (e.g., cholangitis) that responded partially to the treatment for community-acquired pneumonia but has now progressed.

On the fourth hospital day, the patient’s condition worsened, with a body temperature of 35.4°C, a respiratory rate of 24 breaths per minute, a pulse of 120 beats per minute, and a blood pressure of 85/50 mm Hg. Worsening hypoxemia necessitated intubation and transfer to the intensive care unit, where a third chest radiograph showed increased patchy infiltrates bilaterally. Multiple cultures of blood and urine were performed, and a test for the human immunodeficiency virus (HIV) was obtained. His antibiotic regimen was changed to include piperacillin–tazobactam and gentamicin. Pulmonary-artery catheterization revealed a cardiac index of more than 5 liters per minute per square meter of body-surface area, a systemic vascular resistance of less than 300 dyn·sec·cm⁻⁵, and a pulmonary-capillary wedge pressure of 15 mm Hg.

Although hepatic dysfunction can cause hypotension, we must assume that the patient has sepsis on the basis of his hemodynamic measurements and hypothermia. The patient either has pneumonia as the cause of these infiltrates with sepsis secondary to pneumonia or has some other cause of sepsis (probably an intraabdominal cause) with pulmonary edema. Pneumonia has been the leading diagnosis from the start and remains so, with an increasing likelihood of a resistant organism. Thus, while I agree with broadening the antibiotic coverage, vancomycin is also indicated for penicillin-resistant pneumococcal infection. I am also concerned about legionella infection, given his nonproductive cough, hyponatremia, and poor response to β-lactam antibiotics and aminoglycosides. Tuberculosis or a fungal infection seems unlikely, given the acute presentation and brief improvement with cefuroxime and doxycycline.
To look for other possible sources of sepsis, I would order an abdominal CT scan and an echocardiogram. One additional possibility is adrenal insufficiency, which may complicate critical illness. In this patient with hypotension, hypothermia, and hyponatremia, I would perform a corticotropin stimulation test or consider measuring the cortisol level in a random serum specimen, but would initiate empirical treatment with corticosteroids while awaiting the result.

The patient remained hypotensive, despite the use of dopamine and phenylephrine hydrochloride, and hypoxemic, despite 100 percent inspired oxygen delivered by a ventilator. All blood and urine cultures and the HIV test were negative. An echocardiogram was notable only for hyperdynamic left ventricular function, without wall-motion abnormalities. Abdominal ultrasonography revealed a thickened gallbladder wall with pericholecystic fluid but no stones and normal hepatic and biliary ducts. Further radiographic studies or bronchoscopy was not performed, because of the patient’s unstable clinical condition. His hemoglobin level decreased to 6 g per deciliter. He passed large amounts of black stool that were guaiac-positive. His blood pressure continued to drop, despite aggressive fluid support and use of vasopressor medications. The patient died on the sixth hospital day. An autopsy was performed.

The patient’s subsequent deterioration did not undermine the initial diagnosis of pneumonia but shifted concern to a resistant organism — penicillin-resistant Streptococcus pneumoniae, multidrug-resistant Haemophilus influenzae, Pseudomonas aeruginosa, or legionella. The tempo of the illness still seemed quick for tuberculosis or fungal infection. I expect the autopsy to reveal pneumonia and hope that tissue cultures identify the organism.

The autopsy revealed a normal gallbladder and bile ducts and a slightly enlarged liver with micronodular cirrhosis. Evidence of a previous myocardial infarction, congestive hepatopathy, and diffuse alveolar damage with pulmonary edema and hyaline membranes were present. There was blood in the stomach and small bowel. Pathological specimens from the lungs (Fig. 2A), mediastinal lymph nodes (Fig. 2B), liver, and kidney showed necrotizing granulomas, with acid-fast bacilli appreciable in some specimens, a finding that is diagnostic of systemic tuberculosis infection. Both adrenal glands had extensive involvement of necrotizing granulomas as well (Fig. 2C). Examination of the brain and spinal cord revealed no acute abnormalities. Two physicians involved in the patient’s care subsequently had positive tests with purified protein derivative for mycobacterium exposure. Their chest radiographs were normal, and they received six months of prophylactic therapy.

**COMMENTARY**

Although the severe acute respiratory syndrome (SARS), West Nile virus infection, anthrax, and infections with various poxviruses are claiming the attention of patients and physicians, tuberculosis remains a major cause of morbidity throughout the world. In 2002, tuberculosis was responsible for more than 2 million deaths worldwide and, in 2001, more than 15,000 infections in the United States. However, if tuberculosis is not considered, it will not be diagnosed. In retrospect, the diagnosis of tuberculosis warranted consideration in a marginally housed, elderly man with probable chronic liver disease. As the discussant points out, the lack of response to the initial antibacterial therapy also indicated the need for further consideration of atypical infections, among them tuberculosis.

This diagnosis, however, was far from straightforward. The original presentation did not obviously indicate tuberculosis. Clinicians often try to find simple explanations to expedite the evaluation and care of elderly patients found incapacitated. Here, the clinicians considered common causes, such as urinary tract infection, pneumonia, electrolyte abnormalities, and cardiovascular events, and treated the patient empirically for a bacterial pneumonia. In one study of patients who were found helpless or dead in their homes, one out of three patients had an infection. Neurologic events and cardiac disorders were the next most likely causes of being found in this state. Unless the cause is obvious, all these possibilities should be evaluated. Aside from pneumonia, other causes, including a neurologic event, warranted greater attention in this case. Early evaluation of hepatic encephalopathy, stroke, or a central nervous system infection (due to subacute meningitis, for example) would have been appropriate though unlikely to lead to the correct antemortem diagnosis.

Initially, the patient’s condition seemed to improve. Dehydration and malnutrition can compli-
cated many disease processes, especially infections, and correction of these problems can result in apparent improvement, while the underlying cause remains untreated. Such improvements should not curtail the evaluation of other diagnoses. As noted by the discussant, adrenal insufficiency warranted consideration when the patient remained hypotensive. The threshold for evaluating and empirically treating adrenal insufficiency in critically ill patients should be low, given an incidence as high as 40 percent in this population. Although cortisol levels were not measured, the diffuse involvement of the adrenal glands that was apparent at autopsy suggests that adrenal insufficiency due to tuberculosis probably complicated the patient’s illness. Tuberculosis remains an important cause of primary adrenal insufficiency.

This case highlights the value of autopsy. Unfortunately, the autopsy rate continues to decline in the United States; in 1994, the most recent year for which figures are available, autopsies were performed after only 6 percent of deaths in nonforensic cases. Yet there continues to be a large discrepancy between clinical diagnoses and autopsy findings, with a median major-error rate of 24 percent. Without an autopsy, the patient’s clinicians would have neither recognized their exposure to tuberculosis nor had the opportunity to learn in order to improve the care of future patients. The possibility that an autopsy will unearth important clinical information is sufficiently high that initiatives to improve autopsy rates are needed.

Finally, it is important to remember that tuberculosis has varying clinical manifestations, especially when infection is widely disseminated. The discussant considered but rejected tuberculosis as a diagnosis, because the clinical course was too quick. Although miliary tuberculosis commonly has a subacute presentation, it may be manifested as a syndrome of rapidly progressing multiorgan dysfunction with sepsis or as the acute respiratory distress syndrome. Miliary tuberculosis is more common among immunocompromised patients, including those with the acquired immunodeficiency syndrome, children under the age of five years, and the elderly. The mortality associated with miliary tuberculosis approaches 50 percent. Because miliary tuberculosis reflects hematogenous spread of the mycobacterium, it typically affects multiple organs (e.g., the liver, spleen, and adrenal glands), with central nervous system involvement in up to 20 percent of patients. Though miliary tuberculosis derives its name from the tiny, discrete granulomas resembling millet seeds seen on chest radiography, the chest radiograph is interpreted as normal in approximately 40 percent of cases. Transmission to others is uncommon but may have occurred in this case.
Clinical Problem-Solving

Although not as headline-grabbing as SARS or West Nile virus infection, tuberculosis remains a major cause of morbidity and mortality throughout the world and in the United States. With rising numbers of elderly people and the increasing rate of chronic immunosuppression, clinicians should consider the possibility of tuberculosis even if the clinical manifestations and presentation are atypical.

Supported by a National Research Service Award from the Agency for Healthcare Research and Quality (to Dr. Jha) and a Career Development Award from the Health Services Research and Development Program of the Department of Veterans Affairs and a Patient Safety Developmental Center Grant (P20HS11540) from the Agency for Healthcare Research and Quality (both to Dr. Saint).

We are indebted to Henry Holdt for his critical aid in obtaining pathological and radiologic data.

References


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