

CLINICAL CARE CONUNDRUM

“Making a List and Checking It Twice”

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.

Satyen Nichani, MD¹
Sandro Cinti, MD²
Jeffrey H. Barsuk, MD³

¹Division of General Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

²Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

³Division of Hospital Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

In October, a 36-year-old woman with no significant past medical history presented to the Emergency Department (ED) with a 3-day history of headache and fever. The headache was severe, throbbing, and frontal in location. She also complained of daily fevers measured up to 103°F, generalized malaise, and fatigue. She did not report neck stiffness or photophobia. She felt better after receiving intravenous fluids and was discharged home with a diagnosis of a nonspecific viral illness. Two days later, she returned to the ED with worsening headache, fever, mild photophobia, and poor oral intake. She also complained of a dry cough that made her headache worse, as did bending over. She did not report confusion, neck stiffness, shortness of breath, sore throat, runny nose, abdominal symptoms, or rash.

This patient presents a second time to the ED with worsening headache and fever raising concerns about meningitis. At the time of her first ED visit, it can be assumed that she had a nontoxic appearance because she was discharged shortly thereafter. Thus, acute bacterial meningitis seems less likely, but occasionally patients with meningococcal meningitis may not appear significantly ill until later in the process. Nonetheless, acute meningitis, possibly viral, is the initial concern. The time of the year is an important variable because many viral infections are seasonal. Enteroviruses are the most common cause of viral meningitis in the United States, particularly in the summer and fall. In contrast, mumps, measles, and varicella zoster viruses occur more commonly in winter and spring. Herpetic meningoencephalitis is a life-threatening condition with a guarded prognosis. Therefore, early recognition and treatment is necessary to decrease morbidity and mortality. Drugs such as nonsteroidal anti-inflammatory agents, trimethoprim-sulfamethoxazole, amoxicillin, and rarely vaccines can also cause aseptic meningitis. Infections from fungi, spirochetes, mycobacteria, and rarely parasites also cause meningitis, but would be of greater concern in a patient with risk factors such as recent travel or an immunocompromised state.

Increased headache with bending and cough might indicate elevated intracranial pressure. However, this is a nonspecific complaint, and headache is often worse with the Valsalva maneuver. Because she reports a cough, a chest x-ray would be useful. In addition to routine initial tests,

cerebrospinal fluid (CSF) analysis and human immunodeficiency virus (HIV) testing is recommended.

Her past medical history was notable for depression. Her medications included bupropion, multivitamins, and fish oil. She was also taking milk thistle pills daily to “protect her liver” because she had been drinking alcohol heavily for the past 2 weeks since her husband left her. She smoked 1 pack of cigarettes daily. She had not traveled recently. She reported no recent animal or wildlife exposure but did recall falling into a midwestern river while canoeing 2 weeks prior to presentation. She worked as a hairstylist and described no sick contacts or risk factors for HIV disease.

An important new historical element is that the patient fell into a river. If she swallowed a significant amount of water during her fall overboard, meningitis from waterborne infections such as *Aeromonas*, *Acanthamoeba*, and *Naegleria* need to be considered. Fortunately, these are rare in the Midwest. Her canoeing history may suggest exposure to wooded areas. Certainly, tickborne infections such as ehrlichiosis, babesiosis, Lyme disease, and Rocky Mountain spotted fever can also cause meningitis. Histoplasmosis and blastomycosis are also endemic to the midwestern United States and can disseminate and cause central nervous system disease.

At this time, viral and bacterial infections are highest on the differential diagnosis. However, the microbiology laboratory needs to be alerted to the possibility of fungal or parasitic organisms depending on the initial CSF analysis results.

The patient was a Caucasian woman who appeared comfortable. Her blood pressure was 130/62 mm Hg, heart rate was 83 beats per minute, respiratory rate was 18 per minute, temperature was 100.8°F, and oxygen saturation was 98% on room air. She was fully alert and oriented. Her pupils were bilaterally equal, reactive to light and accommodation with intact extraocular movement and no nystagmus. There was conjunctival injection bilaterally without noticeable pallor or icterus. Fundoscopic examination, which the patient tolerated without difficulty, was normal. Inspection of the oral cavity showed mild tonsillar enlargement. The neck was supple with no stiffness. No cervical, axillary, or inguinal lymph nodes were palpable. Faint bilateral basilar crackles were audible over the posterior chest. There was very mild right upper quadrant abdominal tenderness without guarding. The

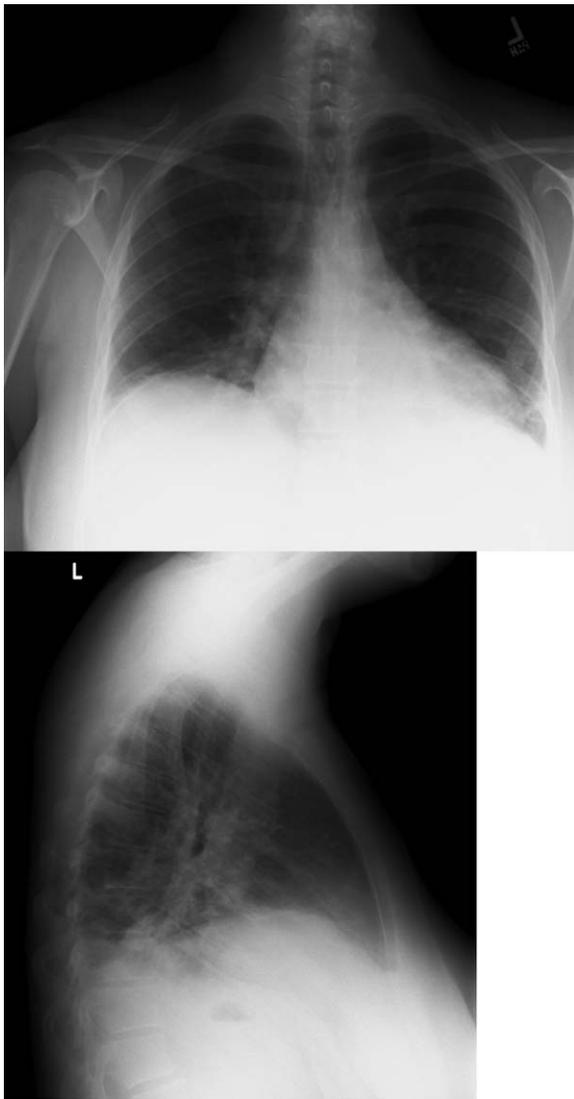


FIGURE 1. Admission chest x-ray (postero-anterior [upper panel] and lateral [lower panel] views).

liver and spleen were normal size and bowel sounds were present. No rash, peripheral edema, or spinal tenderness was noted. A complete neurological examination was normal.

Her general appearance and vital signs seem reassuring. Conjunctival injection and mild tonsillar enlargement are nonspecific findings and may occur in systemic inflammatory states especially viral infections. Atelectasis may account for faint bilateral basilar crackles especially if associated with post-tussive change. Her alcohol use puts her at risk of aspiration. A right lower lobe process (pneumonia) can sometimes present with right upper quadrant tenderness. However, this tenderness may also represent muscle soreness from repeated coughing, liver, or gallbladder disease. The same infectious process affecting the central nervous system and possibly her lungs, may also be affecting the liver.

A complete blood count revealed a white blood cell count of $3000/\text{mm}^3$ (79% neutrophils, 15% lymphocytes, 5% monocytes), hemoglobin of 11.7 g/dL, and platelets of $110,000/\text{mm}^3$. The serum sodium was 133 mmol/L, potassium was 3.7 mmol/L, bicarbonate was 22 mmol/L, and blood urea nitrogen was 20 mg/dL. The serum creatinine was 1.5 compared to 1.0 mg/dL on testing 2 days prior. A liver function panel showed protein of 5.1 g/dL, albumin of 3 g/dL, aspartate aminotransferase (AST) of 576 IU/L, alanine aminotransferase (ALT) of 584 IU/L, alkaline phosphatase of 282 IU/L, and total bilirubin of 1 mg/dL. The coagulation profile, creatinine phosphokinase, acetaminophen level, urine pregnancy test, urine drug screen, and urinalysis (including urine microscopy) were normal.

The CSF opening pressure was 13 cm H₂O. CSF analysis showed 4 mononuclear leukocytes per high-power field, CSF protein was 27 mg/dL, and glucose was 76 mg/dL. No organisms were noted on gram stain. A chest x-ray showed focal airspace opacity in the left lower lobe (Figure 1) and the patient was hospitalized for further management.

The normal CSF analysis makes acute meningitis much less likely. It is interesting to note that the aminotransferase levels are nearly equal. Usually, in viral and many other causes of hepatitis, the ALT is higher than the AST, whereas the contrary is true in alcoholic hepatitis. Because the patient has been consuming significant amounts of alcohol recently, these levels may become equal in the setting of another primary liver process. The elevation in liver enzymes also raises the possibility of autoimmune hepatitis secondary to a systemic vasculitis such as systemic lupus erythematosus. Nonetheless, the focus should be on infectious causes of hepatitis such as hepatitis C, adenovirus, parvovirus, Epstein-Barr virus (EBV), cytomegalovirus, and herpes simplex virus that can cause pneumonia either as a primary or secondary infection. Acute HIV infection can also present in this fashion, and anti-HIV antibody testing may be negative early in the disease. In the setting of a normal urinalysis and bland urine sediment, prerenal azotemia is the most likely cause of her acute renal injury and can be confirmed by testing the urinary sodium and creatinine. A peripheral smear should be reviewed to evaluate the pancytopenia.

Severe headache, fever, conjunctival injection, pancytopenia, acute kidney injury, hepatitis, and pneumonia may occur in leptospirosis, particularly in a patient with recent freshwater exposure. Alternatively, ehrlichiosis can also account for fever, headache, pancytopenia, renal failure, hepatitis, and pneumonia, but conjunctival suffusion is not often present. At this time, treatment for community-acquired pneumonia that includes coverage for leptospirosis should be started.

The patient was hydrated with intravenous fluids and treated with intravenous ceftriaxone and azithromycin for community-acquired pneumonia. An abdominal ultrasound was normal. The serologic assays for acute hepatitis A, B, and C infection were negative. The

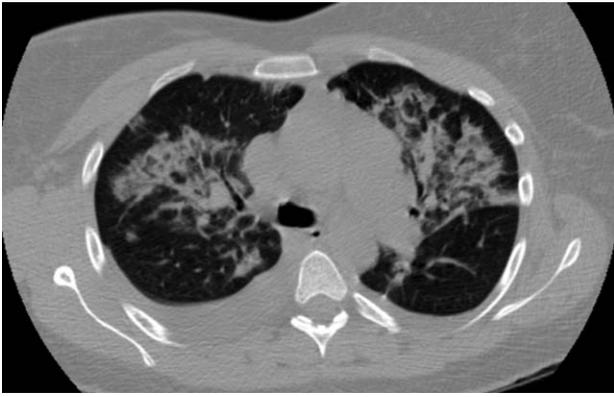


FIGURE 2. Bilateral patchy airspace disease and pleural effusions on chest computed tomographic scan.

following morning, she reported worsening headache, increased cough now productive of whitish-yellow sputum, and diffuse body aches. She appeared more lethargic and toxic. Her blood pressure was 100/83 mm Hg, heart rate was 84 beats per minute, respiratory rate was 24 per minute, and temperature was 101.3°F. She had increased crackles on chest auscultation bilaterally and required supplemental oxygen at 4 L/minute by nasal cannula. Examination of both legs now revealed multiple scattered, faintly erythematous, 2-cm-sized patches overlying tender subtle subcutaneous nodules. Additionally, a mildly pruritic, V-shaped area of blanchable erythema was also seen on her chest. The white blood cell count was 2500/mm³ (77% neutrophils, 15% lymphocytes), serum creatinine was 1.8 mg/dL, AST was 351 IU/L, and ALT was 485 IU/L. Blood cultures showed no growth and a peripheral smear examination was unrevealing. A noncontrast chest computed tomographic scan showed findings consistent with multifocal pneumonia (Figure 2).

It would be prudent at this time to expand her antimicrobial coverage (such as with vancomycin and piperacillin-tazobactam) for activity against methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* because of her clinical worsening. Although ceftriaxone or piperacillin would cover leptospirosis, given the possibility of ehrlichiosis, the addition of doxycycline should be strongly considered.

The description of the rash on her legs seems consistent with erythema nodosum, which is associated with a number of infections (streptococcal, fungal, syphilis, EBV, cat-scratch disease, tuberculosis), inflammatory conditions (inflammatory bowel disease, autoimmune disease, malignancy), and pregnancy. The blanchable rash on the chest is also a cause of concern for a possible drug reaction (ceftriaxone). A Jarisch-Herxheimer reaction is possible given her acute worsening of symptoms with initiation of antibiotic therapy.

An antineutrophil cytoplasmic antibody-associated vasculitis or another autoimmune condition such as systemic lupus erythematosus can account for erythema nodosum, rash, pancytopenia, and hepatitis. This diagnosis might also fit if she had a vasculitic pulmonary hemorrhage that caused her lung infiltrates and worsening hypoxia. A com-

plete antinuclear antibody panel, antineutrophil cytoplasmic antibody, and anti-smooth muscle antibody testing is recommended. A skin and bronchoscopic biopsy should be considered.

Her dose of ceftriaxone was increased for possible severe pneumococcal pneumonia. The dermatology consultant felt that her leg lesions were consistent with erythema nodosum and the chest rash consistent with cutaneous photodamage. Bronchoscopic examination was normal and a bronchoalveolar lavage sample showed 2905 red blood cells/mm³ and 605 white blood cells/mm³ (70% neutrophils, 7% lymphocytes, 16% histiocytes), normal cytology, and negative cultures. There was no significant clinical improvement by the fourth hospital day and oral doxycycline was started. The next day, her skin lesions had resolved and she felt better. The serologic tests for *Legionella*, *Mycoplasma*, cytomegalovirus, EBV, *Toxoplasma*, *Chlamydia*, *Ehrlichia*, *Leptospira*, Q-fever, parvovirus, and adenovirus were negative. A fungal serology panel, HIV polymerase chain reaction, cryoglobulin level, and several rheumatologic tests (antinuclear antibody, extractable nuclear antigen panel, rheumatoid factor, antineutrophil cytoplasmic antibody, anti-proteinase 3, and anti-glomerular basement membrane antibodies) were normal. Blood cultures continued to show no growth.

The apparent response to doxycycline suggests she might have ehrlichiosis. A buffy coat review for morulae should be done. It is also possible that she may have improved on her initial therapy alone before starting doxycycline and her clinical worsening (including the chest rash) was due to a Jarisch-Herxheimer reaction. Serologic tests for leptospirosis and ehrlichiosis should be repeated in 1–2 weeks because such infections may not cause detectable antibody levels early in the illness.

Ceftriaxone and doxycycline were continued and she showed rapid and significant clinical improvement. She was discharged 4 days later with instructions to complete a 10-day course of antibiotics. At her 3-month follow-up, she was doing well and a repeat *Leptospira* antibody test by the Indirect Hemagglutination Assay (MRL Diagnostics, Cypress, California; normal titer <1:50) was positive at a titer of 1:100, which is highly suggestive of leptospirosis.

Commentary

Leptospirosis is a zoonotic infection caused by spirochetes of the genus *Leptospira*. The infection is usually transmitted indirectly to humans through contact with water, food, or soil contaminated with the urine of infected mammals.¹ Risk factors for infection include participation in recreational activities (such as freshwater swimming, canoeing, and camping), occupational exposure, and exposure to infected pets or domesticated livestock. Approximately 100–200 cases are identified annually in the United States, and approximately half occur in the state of Hawaii.² Outbreaks of leptospirosis have been reported previously in the Midwest.³

TABLE 1. Clinical Manifestations of Leptospirosis^{1,4,5}

1. Mild influenza-like self-remitting disease (90% of cases)
 - Undifferentiated *fever* (usually 100°F–105°F), severe *headache*, and *myalgia* (especially lower limbs).
2. Moderately severe disease usually requiring hospitalization (5%–9% of cases)
 - Marked prostration, anorexia, nausea, and vomiting, *conjunctival suffusion*, *transient rash*, frequently abdominal pain, constipation or diarrhea, and occasionally epistaxis.
3. Severe disease involving multiple organ systems (1%–5% of cases)
 - *Hepatorenal Syndrome (Weil's syndrome)*
Constellation of jaundice, hemorrhagic diathesis, and *acute renal failure*. Hepatic failure is rarely fatal. Renal involvement is usually more severe and the common cause of death. Cardiac (myocarditis with arrhythmias) and *pulmonary complications* are frequent. Confusion and restlessness may occur.
 - Hemorrhagic pneumonitis
Usually presents as a dry cough initially but becomes blood-streaked after 2–3 days. Often characterized by a rapid progression to involve extensive areas of lungs, massive intra-alveolar hemorrhage, acute respiratory failure, and death.
 - Central nervous system involvement
Meningismus, meningitis, or meningoencephalitis.

NOTE: This patient's manifestations are highlighted in italics.

These organisms inoculate humans through contact with mucous membranes or broken skin, or enter by swallowing infected food or water. A large number of these infections remain subclinical or result in a very mild illness with spontaneous clearance by the host's immune mechanism. Following an incubation period of 2–30 days, infected individuals may develop clinically significant disease (Table 1). Clinical presentations may overlap as the disease progresses. Although much remains to be learned about the exact pathogenic mechanism, disruption of the cell membranes of small vessel endothelia (a toxin-like effect), and cytokine-mediated tissue injury are believed to cause organ hemorrhage and ischemia.⁴

The clinical diagnosis of leptospirosis is difficult because of its protean manifestations. Although nonspecific, 2 clinical features may provide a clue to the clinical diagnosis. First, the presence of conjunctival suffusion occurs in the early stage of the disease and is often associated with subconjunctival hemorrhage. Second, severe myalgia, commonly involving the lower limbs, is also characteristically present.^{1,5} In 1 series of 58 patients with acute leptospirosis, conjunctival suffusion was observed in 50% of cases, and subconjunctival hemorrhage in 29%. Body ache and muscle tenderness was described in almost all cases.⁶

As seen in this case, the presence of a rash may pose a clinical challenge. A transient macular, maculopapular, purpuric, or urticarial rash may be seen in acute leptospirosis, but rashes may also be representative of a complication of treatment.¹ First described in 1895 in patients with syphilis treated with mercury, the Jarisch-Herxheimer reaction typically occurs within a few hours of antimicrobial treatment of spirochete infections and often presents with a rash, headache, fever, rigors, hypotension, sweating, and worsening symptoms of the underlying illness.⁷ Other skin findings

such as the occurrence of erythema nodosum have been previously reported in cases of leptospirosis.⁸

Human ehrlichiosis (HE) is caused by tickborne, obligate intracellular bacteria that infect leukocytes. There are 3 distinct clinical conditions: human monocytic ehrlichiosis (HME, caused by *Ehrlichia chaffeensis*), human granulocytic anaplasmosis (HGA, caused by *Anaplasma phagocytophilum*), and human ewingii ehrlichiosis (HEE, caused by *E. ewingii*). Although most cases of HME and HEE are seen in the southeastern and south-central United States and California, the highest incidence of HGA is reported in the northeastern and upper Midwest regions.⁹ As with leptospirosis, the clinical range of HE spans from asymptomatic infection to life-threatening illness. Following an incubation period of 1–2 weeks, symptomatic cases usually present with nonspecific complaints such as high fevers, chills, headache, nausea, arthralgia, myalgia, and malaise.¹⁰ The majority of cases will report a tick bite or an exposure to ticks. Laboratory tests often reveal leukopenia (white blood cell count < 4000/mm³), thrombocytopenia, hyponatremia, and elevated AST and ALT. Patients with severe disease may develop renal, respiratory, and hepatic failure. Thus, differentiating ehrlichiosis from leptospirosis is often challenging for the clinician.

However, there are a few clinical clues that help distinguish between these illnesses in this case. HGA as a cause of HE would be more likely in the Midwest. Although a rash is present in one-third of patients with HME, it is seldom present in HGA unless coinfecting with *Borrelia burgdorferi*, the causative agent for Lyme disease. Additionally, her history of freshwater exposure and the absence of a history of a tick bite also favor leptospirosis. As noted previously, conjunctival suffusion, a characteristic clinical feature of leptospirosis, has only been described in case reports of HE.^{11,12}

Serologic tests are often used to establish the diagnosis of leptospirosis and ehrlichiosis. Leptospire are fastidious organisms that are difficult to isolate on inoculated growth media. The microscopic agglutination test for leptospirosis is considered the diagnostic gold standard due to its high specificity, but its use is limited by its technical complexity, lack of availability (other than in reference laboratories), and low sensitivity early in the disease (antibody levels detected by this method usually do not appear until 7 days after symptom onset).¹³ A variety of rapid serologic assays are also available. Although these tests have good overall sensitivity (ranging between 79% and 93%), they perform relatively poorly for acute-phase sera (sensitivity of 38.5%–52.7%).¹³ The high early false negative rate is believed to be a result of inadequate *Leptospira* antibody titers in the acute phase of the illness. Seroconversion or a 4-fold rise between acute and convalescent-phase antibody titers is the most definitive criterion for the diagnosis of leptospirosis. However, without paired sera samples, a single high microscopic agglutination test titer can be taken as diagnostic for leptospirosis depending on the degree of regional endemicity.¹⁴

Similarly, currently available serologic assays for ehrlichiosis produce negative results in most patients in the first week of illness, and it is important to obtain a convalescent phase serum specimen for confirmatory diagnosis of HME and HGA. Seroconversion or a 4-fold increase in titer between acute and convalescent phase sera is considered diagnostic. The sensitivity of finding morulae (intracytoplasmic vacuolar microcolonies of *Ehrlichia*) on a peripheral smear is unknown, and data suggest that this finding is more common in cases of HGA compared to HME.¹⁵

Although doxycycline is the drug of choice for the treatment of ehrlichiosis, *Leptospira* is susceptible to a wide variety of antibiotics because it exhibits a double membrane surface architecture with components common to both gram-negative and gram-positive bacteria.¹ Recommended treatment regimens for severe leptospirosis include the use of high-dose intravenous penicillin or a third-generation cephalosporin. Less severe cases can be treated with oral amoxicillin or doxycycline.¹⁶ The fact that this patient's clinical improvement appeared to lag after initiation of ceftriaxone does not necessarily indicate a lack of efficacy but perhaps a Jarisch-Herxheimer reaction in response to appropriate antibiotic therapy.

Teaching Points

1. Establishing a diagnosis of leptospirosis is challenging and requires a high index of suspicion. Clinicians should be aware of the limitations of the diagnostic accuracy of the serologic assays for leptospirosis because they are frequently negative in the first week after symptom onset.
2. The classic finding of conjunctival suffusion is helpful in differentiating leptospirosis from human ehrlichiosis.
3. This case also highlights the importance of the clinical practice of making a list of suspected diagnoses, remaining open to these possibilities, and checking serologic tests again in convalescence to confirm the diagnosis.

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Address for correspondence and reprint requests:

Satyen Nichani, MD, 3119 Taubman Center, SPC 5376, 1500 East Medical Center Drive, Ann Arbor, MI 48109; Telephone: 734-647-6928 Fax: 734-232-0840; E-mail: satyen@umich.edu Received 28 April 2010; revision received 20 September 2010; accepted 15 October 2010.

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