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Spiraling Out of Control

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Abstract

A 22-year-old man presented to the emergency department on Christmas Day with a 5-day history of myalgias, cough, dyspnea, nonbilious emesis, and nonbloody diarrhea. Although he had been ill for several days, he ultimately sought treatment because of intractable vomiting. He reported feeling feverish, although he had not measured his temperature, and noted one episode of hemoptysis.

A subacute presentation of fever, cough, myalgia, and gastrointestinal symptoms in a young person during respiratory virus season most likely indicates influenza or other viral or bacterial infection, such as *Legionella pneumophila* or *Mycoplasma pneumoniae*. If hemoptysis has truly occurred, this would be an unusual manifestation of these infections, particularly in the absence of a productive cough. The presence of hemoptysis should broaden the differential diagnosis to include aggressive pathogens that could cause both necrotizing pneumonia and systemic symptoms, such as *Staphylococcus aureus*, gram-

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

negative bacilli, and less commonly, *Leptospira interrogans*. The patient should be questioned about behaviors associated with an increased risk of human immunodeficiency virus (HIV) infection and about travel and exposure to animals. The combination of fever and hemoptysis also raises the possibility of noninfectious inflammatory diseases, such as Goodpasture's syndrome, that cause alveolar hemorrhage and may be triggered by infection.

The patient had not received the annual influenza vaccine. He was sexually active with one female partner. He had smoked marijuana and a half pack of cigarettes daily for several years. He did not drink alcohol or use other drugs. He lived in Baltimore with his grandmother and reported no recent travel. He also reported no history of incarceration.

The patient's stable domicile and lack of previous incarceration are important in weighing his risk for exposure to tuberculosis, although the pace of the current illness does not suggest that diagnosis. The possibility of underlying HIV infection should be considered in all sexually active patients and must be addressed early, since immunosuppression profoundly affects the differential diagnosis of pulmonary processes. Cigarette smoking may also confer a predisposition to bronchopulmonary infection. Inhaling marijuana may cause colonization or infection with species of aspergillus and other molds, which may be particularly problematic in immunocompromised patients.

On physical examination, the patient's temperature was 36.4°C (97.5°F), blood pressure 102/50 mm Hg, heart rate 108 beats per minute, respiratory rate 17 breaths per minute, and oxygen saturation 100% while he was breathing ambient air. He appeared to be comfortable. The lungs were clear to auscultation. The abdomen was soft, nontender, and without organomegaly. He had no tenderness at the costovertebral angle.

The white-cell count was 12,650 per cubic millimeter, with 63% neutrophils, 26% bands, and 6% lymphocytes. The hematocrit level was 40%, the mean corpuscular volume 82 fl, and the platelet count 129,000 per cubic millimeter. The serum sodium level was 128 mmol per liter, potassium 3.7 mmol per liter, chloride 83 mmol per liter, bicarbonate 21 mmol per liter, blood urea nitrogen 34 mg per deciliter (12.1 mmol per liter), creatinine 3.9 mg per deciliter (340 μ mol per liter) (1.0 mg per deciliter [88 μ mol per liter] 4 years earlier), glucose 110 mg per deciliter (6.1 mmol per liter), magnesium 1.6 mg per deciliter (0.66 mmol per liter), and calcium 10.1 mg per deciliter (2.52 mmol per liter). The aspartate aminotransferase level was 43 U per liter (reference range, 0 to 37), alanine aminotransferase 31 U per liter, total bilirubin 1.9 mg per deciliter (32 μ mol per liter) (reference range, 0 to 1.2 mg per deciliter [0 to 21 μ mol per liter]), alkaline phosphatase 92 U per liter, and lactate 2.8 mmol per liter (reference range, 0.5 to 2.2). Prothrombin time and partial-thromboplastin time were normal. Respiratory viruses were not detected on a polymerase-chain-reaction (PCR) assay of a nasal-swab specimen. A test for HIV RNA was negative. A urinalysis revealed cloudy, yellow urine with a pH of 5.5, specific gravity of 1.011, 2+ protein, and 4 red cells and 21 white cells per high-power field (reference range, 0 to 5), although the patient reported no dysuria or flank pain. A urine toxicology screening test was positive for cannabinoids.

Because there is no known history of renal disease, the kidney injury is probably acute and related to the current illness. The preceding vomiting and diarrhea may have led to prerenal azotemia; however, the specific gravity of the urine is not elevated. Acute tubular necrosis as a complication of sepsis is also possible, but no tubular casts were reported in the urine sediment. Hemoptysis and acute kidney injury arouse concern for the possibility of noninfectious inflammatory diseases, such as anti-glomerular basement membrane disease, systemic lupus erythematosus, and vasculitides, but the patient does not have appreciable hematuria. Instead, the sediment contains an elevated number of leukocytes, but neither the examination nor his symptoms suggest pyelonephritis or sexually transmitted infection. With exclusion of other causes, the combination of pyuria and acute kidney injury leads to consideration of tubulointerstitial nephritis, which can be caused by a variety of drugs, inflammatory processes, and less commonly, infections, of which leptospirosis is one.

Nine hours later, the patient's blood pressure decreased to 59/31 mm Hg, despite aggressive volume resuscitation. His temperature was 38.3°C (100.9°F), heart rate 120 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation 95% while he was breathing ambient air. Blood cultures were obtained, and vancomycin, cefepime, metronidazole, azithromycin, and oseltamivir were initiated, as was norepinephrine. Computed tomography of the chest, abdomen, and pelvis without contrast showed diffuse bronchial-wall thickening and tree-in-bud nodularity (Fig. 1).

A tree-in-bud pattern suggests bronchial disease, with debris filling the airways. The most common causes are infection and aspiration, which account for more than 80% of cases. Although indolent infections from mycobacterial and fungal pathogens are among the possible causes, a viral or bacterial infection is much more compatible with the time course of this patient's illness. A respiratory viral PCR assay was negative, but false negative results for influenza occur in up to 10% of cases; in a patient whose condition is unstable, it is justifiable to continue empirical therapy with a neuraminidase inhibitor.

Among bacterial respiratory pathogens, typical pyogenic organisms, such as *Streptococcus pneumoniae*, are unlikely to cause severe sepsis without obvious pneumonia. "Atypical" bacteria, including *Bordetella pertussis*, *L. pneumophila*, and *M. pneumoniae*, may cause bronchitis and radiographic findings similar to the findings in this patient and occasionally cause this degree of systemic toxic effects. The latter two pathogens have also been associated with acute interstitial nephritis. Although leptospirosis would fit many elements of the current presentation, such as severe systemic illness associated with hemoptysis, renal failure, and hyperbilirubinemia, hemoptysis in this condition results from diffuse alveolar hemorrhage, which the chest imaging does not suggest.

Urine and blood cultures remained negative. A sputum culture revealed respiratory flora; stains of expectorated sputum were negative for acid-fast bacilli. Stool tests were negative for enteric pathogens, ova, and parasites. Tests for antinuclear antibodies, IgG antibodies to the glomerular basement membrane, mononucleosis, and syphilis (treponemal test) were all negative, as were tests for IgG and IgM antibodies to parvovirus and Q fever, and IgM antibodies to leptospira. Tests for hepatitis A and C antibodies and for hepatitis B surface antigen and core antibody were all negative. IgG and IgM antibodies to influenza type A

were detected by means of complement fixation testing at a titer of 1:16 (reference range, <1:8); tests for antibodies to influenza type B were negative. A urine test for legionella antigen and a sputum culture for legionella were both negative. An interferon gamma release assay (IGRA) for tuberculosis was positive.

In a desperately ill patient, it is common to order a broad array of tests, but the results must be interpreted critically, with consideration of the pretest likelihood of a given disease and the performance characteristics of the chosen tests. In this case, since the viral respiratory PCR assay was negative, the low-positive serologic findings of antibodies to influenza type A probably represent a false positive result owing to a recent incidental influenza infection or a lingering response to more remote infection or immunization. Conversely, serologic results for infections may be negative if titers are measured early in the course of illness.

Because tuberculosis can cause culture-negative sepsis, the interpretation of the positive IGRA result is crucial. A positive IGRA does not distinguish between latent and active tuberculosis. The rapid progression of this patient's disease and the absence of known immunodeficiency do not support active tuberculosis as the cause of the current presentation. Although tuberculosis is a classic cause of tree-in-bud changes, these changes almost always occur in conjunction with a parenchymal lung infection.

The patient was admitted to the intensive care unit. Respiratory distress developed; his respiratory rate was 30 breaths per minute, and the oxygen saturation 85% with 4 liters of supplemental oxygen administered through a nasal cannula. The white-cell count was 14,500 per cubic millimeter (with 73% neutrophils, 14% bands, and 3% lymphocytes), the hematocrit 31%, and the platelet count 84,000 per cubic millimeter. The peripheral blood smear showed normochromic anemia with echinocytes, thrombocytopenia, and increased levels of immature neutrophil forms, with Dohle bodies, toxic granules, and cytoplasmic vacuoles noted. The potassium level was 3.4 mmol per liter, bicarbonate 15 mmol per liter, creatinine 3.5 mg per deciliter (309 μ mol per liter), lipase 1171 U per liter (reference range, 16 to 63), ferritin 841 μ g per liter (reference range, 30 to 400), and lactate 2 mmol per liter. The aspartate aminotransferase level was 65 U per liter (reference range, 0 to 37), alanine aminotransferase 34 U per liter, and total bilirubin 3.0 mg per deciliter (51 μ mol per liter) (direct bilirubin, 2.9 mg per deciliter [50 μ mol per liter]). A radiograph of the chest revealed significantly increased patchy infiltrative changes involving both lungs (Fig. 2).

During a complicated hospital course, it may be difficult to determine whether new findings represent progression of the underlying disease process or treatment complications. The differential diagnosis for the interval development of worsening hypoxemia and airspace disease in both lungs includes worsening of a respiratory infection, aspiration pneumonitis, circulatory overload due to aggressive volume resuscitation, and acute lung injury due to sepsis. The time course is early for the development of health care-associated pneumonia. Since the time of admission, the patient has had a slight increase in the aspartate aminotransferase level and an increase in the bilirubin level, which could be a result of a direct infection of the liver or of cholestasis associated with sepsis. Whereas macro-lide antibiotics may cause a similar pattern of abnormalities, these toxic effects typically occur later during the course of therapy. Because the elevated bilirubin level is largely conjugated,

it does not support a diagnosis of hemolytic anemia to explain the decrease in the hematocrit level.

The most striking new clinical finding is the markedly elevated lipase level. The absence of risk factors (e.g., alcohol use or gallstone disease) and of abdominal pain at the time of presentation, in addition to the prodrome of fever, cough, and myalgias, does not support a diagnosis of severe acute pancreatitis. Pancreatitis may be part of the multisystem process that is occurring in this patient. Infections or inflammatory processes, such as vasculitis or lupus, may cause a subacute febrile illness that involves the lung, pancreas, gastrointestinal tract, and kidneys. In this previously healthy man, more likely possibilities include an unusually severe viral infection, such as adenovirus or one of the “atypical” pathogens already mentioned — *L. pneumophila*, *M. pneumoniae*, or *L. interrogans*. Legionellosis (Legionnaires’ disease) rarely manifests with such severe disease in a young patient who has no coexisting conditions. Severe leptospirosis (Weil’s syndrome or Weil’s disease) usually manifests with more marked hyperbilirubinemia and amino-transferase elevations than those seen in this patient. Unless a compelling history of water or rodent exposure is elicited, *M. pneumoniae* infection would be more common given his age.

Over the course of the ensuing 3 days, the patient’s condition improved substantially. He no longer required vasopressors or supplemental oxygen, and the renal insufficiency resolved. All cultures remained negative. Tests for antibodies to *M. pneumoniae* showed an IgG level of 2.01 (negative value, <0.90), but the IgM level was 101 U per milliliter (negative value, <770). Treatment with vancomycin, cefepime, and oseltamivir was discontinued. Ceftriaxone was initiated and azithromycin continued. The platelet count increased to 226,000 per cubic millimeter, whitecell count to 18,000 per cubic millimeter, and total bilirubin to 13.3 mg per deciliter (227 μ mol per liter), with a direct bilirubin of 11.4 mg per deciliter (195 μ mol per liter). Additional history revealed that he had recently evaded a police officer by running through an alleyway, where he fell and sustained an abrasion to his thigh.

The additional history and clinical information strongly suggest a diagnosis of leptospirosis. Leptospirosis may be acquired by means of several routes, including mucosal or cutaneous inoculation or possibly ingestion of the organism.

In this case, the timing of his injury in the alleyway, which was probably rat-infested, arouses suspicion of cutaneous inoculation as the most likely route of transmission. The rapid abatement of symptoms with antibiotics and the eventual development of profound cholestatic jaundice are consistent with the diagnosis.

After receiving intravenous cephalosporins for 7 days, the patient was discharged home with instructions to complete 14 days of antibiotic therapy with doxycycline for presumed severe leptospirosis. A repeat indirect hemagglutination test for antibodies to leptospira that was sent on hospital day 4 was positive at a titer of 1:200 (positive value, 1:100). At a follow-up appointment 3 weeks after his initial presentation, he was free of symptoms. Testing of convalescent serum obtained at the time of the appointment showed titers of 1:3200 against

L. interrogans (serogroups ictero- haemorrhagiae and Australia), which is diagnostic of leptospirosis. He declined treatment for latent tuberculosis.

COMMENTARY

Leptospirosis is endemic worldwide, although it is most prevalent in tropical and rural environments.¹ Its most important reservoirs are rodents and small mammals, and contact with their urine, often through contaminated water, is the primary route of transmission.² *Leptospira* enters the body through direct cutaneous or mucosal transmission or by aerosolization.² Of the approximately 1 million annual cases worldwide, an estimated 13,000 occur in the United States and Canada.³ In the United States, leptospirosis is most commonly diagnosed among travelers who have returned from areas in which the disease is endemic (particularly Southeast Asia, Central America, and the Caribbean) and among residents of tropical or semitropical regions, with Hawaii having the highest incidence. Water exposure is a key risk, both domestically and abroad, with multiple reported outbreaks associated with adventure races and ecotourism.^{4,5} A risk factor that is less well known is residence in a city that has a large population of rodents; one Baltimore study showed that 65% of live-trapped rats had antibodies to *L. interrogans*.^{1,6,7} Multiple cases of urban leptospirosis infection, in which the presumed mechanism of infection — injury sustained in a rat-infested alleyway or home — is similar to that in this patient, have been documented.^{8,9}

Leptospirosis has a broad range of manifestations, from subclinical illness or mild self-limited disease (approximately 90% of infections) to Weil's syndrome (Weil's disease), which is characterized by renal failure, jaundice, and hemorrhage and has a 5 to 15% mortality rate.² Symptoms develop after an incubation period of 5 to 14 days.² Mild infections are often indistinguishable from other febrile illnesses. The manifestation of severe illness can be variable; some patients have an initial septicemic phase, followed by a reduction in symptoms, and then an immune phase characterized by potentially critical illness, whereas other patients have symptoms that progress directly to fulminant disease.¹

This patient showed many cardinal features of severe leptospirosis: nonoliguric renal failure; marked hyperbilirubinemia (a bilirubin level of up to 30 to 40 mg per deciliter [512 to 684 μ mol per liter] in some cases), with less severe elevations of aminotransferase levels; thrombocytopenia; and pulmonary involvement.¹ The spectrum of pulmonary involvement is broad, but the most serious manifestations are diffuse alveolar hemorrhage and the acute respiratory distress syndrome.⁹ Common symptoms absent in this case are conjunctival suffusion (extreme conjunctival redness without exudate), muscle tenderness, and aseptic meningitis. Nonspecific symptoms, including fever, gastrointestinal upset, headache, cough, and pharyngitis, are also common.^{1,4,5} Infection with icterohemorrhagiae serogroups has been reported to be associated with an increased risk of severe disease or death.^{1,10}

Controversy exists over whether antibiotics decrease the severity of leptospirosis. A review of seven randomized trials showed that the evidence in favor of or against antibiotic therapy in leptospirosis is insufficient; the duration of the disease appeared to be shorter among patients treated with antibiotics than among those who did not receive antibiotics, but the differences were not significant.¹¹ In a retrospective observational study, delayed initiation

of antibiotics (by 2 days or more) was associated with more severe disease.¹⁰ Guidelines and expert opinion support prompt treatment with antibiotics in suspected and confirmed cases.^{12,13} Oral doxycycline is used to treat mild disease, and intravenous penicillin is used to treat severe disease, although a trial that compared ceftriaxone (1 g daily) with penicillin (1.5 million units every 6 hours) for 7 days showed no significant difference in the time to resolution of fever.¹⁴

The diagnosis of leptospirosis can be challenging to confirm. The organism requires specialized culture mediums and grows over a period of weeks.^{1,2} Serologic testing is often negative early in the course of the disease.⁴ PCR-based nucleic acid amplification testing of blood, urine, or cerebrospinal fluid is much more sensitive than culturing and can be performed early in the course of the disease, but such testing is not widely available.¹ Given these limitations, most diagnoses are still confirmed by serologic testing. A single indirect hemagglutination titer of at least 1:200 but less than 1:800 is suggestive of a leptospirosis infection; an infection is confirmed by either a single titer of at least 1:800 or by a convalescent serum specimen titer that is at least four times as high as the titer of an acute-phase serum specimen.¹⁵

In this case, impediments to making the diagnosis included a delay in acquiring relevant exposure history; the absence of some of the most recognizable symptoms of leptospirosis, particularly conjunctival suffusion; and serologic tests that were initially negative. However, the recognition that leptospirosis can cause multisystem illness in a healthy adult, along with specific findings of marked hyperbilirubinemia and pulmonary hemorrhage, ultimately led to the correct diagnosis and a favorable outcome.

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Figure 1. Axial CT Scan of the Chest, Showing Tree- in-Bud Nodularity and Centrilobular Nodules.

An axial computed tomographic (CT) scan of the chest shows diffuse, mild tree-in-bud nodularity and centrilobular nodules involving the right and left upper lobes (Panel A) and lower lobes (Panel B).

Figure 2. Anteroposterior Radiograph of the Chest, Showing Patchy Infiltrates.

An anteroposterior radiograph of the chest, obtained with portable equipment soon after the patient's admission to the intensive care unit, shows patchy infiltrates involving both lungs, with the right lung showing greater infiltration than the left.