

Leptospirosis: A Rare Cause of Multiorgan Failure

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Leptospirosis is an uncommon and potentially lethal disease that is completely curable if diagnosed and treated early. Leptospirosis is a zoonotic disease caused by organisms of the genus *Leptospira*. When humans are infected with *Leptospira*, the clinical spectrum varies from mild febrile illness to severe disease with multiorgan failure and fatal outcome. Because of its clinical polymorphism and the difficulties in making a bacteriologic and serologic diagnosis, leptospirosis is an affliction that often remains undetected.¹ The term *Weil's syndrome* is used to describe severe leptospirosis with evidence of liver and renal failure. This article discusses a case of Weil's syndrome in a patient who presents to the emergency department with signs of liver and kidney failure in the presence of coagulation abnormalities and with evidence of rhabdomyolysis. The clinical picture and treatment of such a case are described. The emergency physician must be aware of this etiology of multiorgan failure so that the diagnosis of leptospirosis can be made and early and specific treatment can be instituted.

CASE PRESENTATION

A 27-year-old man presents to the emergency department of an urban hospital with a 6-day history of loss of appetite, occasional vomiting, and yellowish discoloration of the eyes. Since 10 days before presentation, he has experienced generalized headache, non-productive cough, body ache, and fever. He denies abdominal pain, melena, hematemesis, joint pain, or skin rash. He is taking no medications.

History

Approximately 1 week prior to the development of these symptoms, the patient was in jail for approximately 3 weeks. His medical history, family history, and social history are noncontributory. He denies any history of foreign travel, exposure to animals, heavy physical exertion, unusual food ingestion, or alcohol or drug

use. The patient was tested for HIV 6 months before his current presentation and found to be negative.

Physical Examination

On physical examination, the patient has a temperature of 101.6°F, blood pressure of 110/70 mm Hg, respiratory rate of 24 breaths/min, and tachycardia with a heart rate of 140 bpm. Results of the remaining cardiovascular and respiratory examination are normal. The patient appears dehydrated. His sclera are jaundiced, and the conjunctiva appear suffused.

On abdominal examination, the patient has tenderness in the right upper quadrant. The liver edge is palpable 3 to 4 cm beneath the right subcostal margin. No splenomegaly is evident, and no peritoneal signs are present.

The rectal examination is negative for occult blood. Results of a neurologic examination are normal, and no signs of meningeal irritation are present. His sensorium is well preserved. Significant tenderness is noted bilaterally over his calf and leg muscles.

Emergent Rehydration

While the patient is in the emergency department, his blood pressure drops to 80/60 mm Hg without change in his sensorium. Fluid resuscitation is initiated with 0.9% saline. He receives a total of 750 mL of fluid by the time that the laboratory results became available.

Laboratory Studies

Laboratory studies reveal a creatinine of 6.9 mg/dL and a blood urea nitrogen of 68 mg/dL. The serum sodium concentration is 134 mEq/dL, chloride is

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102 mEq/dL, bicarbonate is 22 mEq/dL, potassium is 4.7 mEq/dL, and glucose is 102 mg/dL. His blood hemoglobin is 10.1 g/dL with a leukocyte count of 9500/mm³, without a significant left shift. The platelet count is 60,000/mm³. The coagulation profile, arterial blood gas, chest radiography, and electrocardiography do not reveal any significant abnormality. The total bilirubin is 24 mg/dL with a direct component of 15.5 mg/dL. The aspartate aminotransferase is 883 U/mL (0 to 40 reference range), the alanine aminotransferase is 206 U/mL (5 to 35 reference range), and the lactic dehydrogenase is 1317 U/mL (85 to 210 reference range). No fragmented cells are seen on peripheral blood smear. The urine is strongly positive for blood on dipstick but no erythrocytes are seen on microscopy. The creatine phosphokinase is 25,807 ng/mL (0 to 165 reference range).

Hospital Admission and Clinical Course

The patient is admitted to the hospital with the diagnosis of hepatorenal syndrome. He is empirically started on a third-generation cephalosporin (ceftriaxone), and fluid resuscitation is continued.

Over the next 24 hours, the patient becomes anuric. He develops pulmonary edema secondary to excessive fluid overload, and he is transferred to the intensive care unit where he undergoes hemodialysis. His pulmonary function, fluid balance, and electrolyte status are monitored aggressively. Blood and urine cultures as well as the hepatitis serology are negative but the *Leptospira* titer is positive at 1:400. The patient's condition dramatically improves 48 hours after the substitution of penicillin for his broad-spectrum antibiotic coverage.

Discharge and Further History

The patient is discharged after a total hospital stay of 3 weeks. At the time of discharge, the liver enzymes, renal function tests, and platelet count are all within normal range. On repeated questioning at follow-up, the patient tells one of the physicians that he had been bitten by a rat approximately 3 weeks prior to the development of his symptoms.

DISCUSSION

Leptospirosis is an uncommon zoonosis of worldwide distribution that is rarely considered in the differential diagnosis in the emergency department. The epidemiology of human infection, in a particular place and at a particular time, is determined by the nature of the human contact, both direct and indirect, with infected animals. The human is usually a dead-end host; person-to-person transmission is extremely rare.

As a systemic infectious disease, leptospirosis is characterized by multiorgan involvement.²

Etiology and Epidemiology

The etiologic agent is the spirochete *Leptospira interrogans*. Approximately 250 serogroups comprising 19 serotypes have been isolated. Disease in the United States is caused by more than 10 serogroups, the most common of which are *icterohemorrhagiae* and *canicola*.²

Most cases of leptospirosis in the United States result from recreational exposure to the urine of infected animals, particularly dogs, livestock, rodents, wild mammals, and cats.³ Young adult men are the group of patients most frequently affected with this disease. In 1994, 38 cases of leptospirosis were reported in the United States. The majority of the cases (23) were reported in the Pacific states, Washington, Oregon, California, Alaska, and Hawaii.⁴

Clinical Course

The incubation period is usually 7 to 13 days, with a range of 2 to 26 days. The duration of the illness varies from less than 1 week to 3 weeks. Leptospirosis is typically a biphasic illness.

First phase. During the initial or leptospiremic phase, the organisms are typically present in the blood. This stage usually lasts 4 to 7 days. The onset is typically abrupt with nonspecific, influenza-like, constitutional symptoms of fever (more than 90% of cases), chills, headache (79% of cases), severe myalgia (71% of cases), and malaise.¹ Occasionally, patients have diarrhea. Pulmonary manifestations, usually cough and chest pain, vary in incidence from 25% to 76%.¹ Examination during this phase reveals an acutely ill febrile patient with a relative bradycardia and normal blood pressure. Disturbances in sensorium may occur in up to 25% of patients.

Liver syndrome with hepatalgia and pain on mass movement of the liver are present in approximately 60% of cases. Jaundice occurs in approximately 28% of cases.¹ The combination of marked elevation in serum creatine phosphokinase with only modest elevation in serum transaminase may help to distinguish this disease from other forms of acute hepatitis.⁵

Biological renal syndrome, evidenced by transient renal insufficiency with proteinuria, hematuria, and leukocyturia is commonly seen in the first phase of leptospirosis. Acute renal failure requiring dialysis may occur. Rhabdomyolysis may play a significant role in the pathogenesis of acute renal failure, but a correlation between serum myoglobin and severity of renal disease has not been established.⁶

Neurologic manifestations are primarily those of encephalitis and occur in 5.8% of cases.¹ Hemorrhage occurs in less than 10% of cases in the form of bleeding from the gastrointestinal tract, hemoptysis, and epistaxis.¹

Weil's syndrome refers to severe leptospirosis with jaundice and renal involvement. Conjunctival suffusion, the most characteristic clinical finding of Weil's syndrome, occurs in less than 50% of patients. Less common findings may include pharyngeal injection, macular skin rash, and cutaneous hemorrhage.

Second phase. The second phase is an immune phase characterized by the appearance of circulating immunoglobulin M antibodies. After a relatively asymptomatic period of 1 to 3 days, the fever and earlier symptoms recur. The fever may be transient or low grade. Signs of meningism may appear. Less common features include encephalitis, iridocyclitis, optic neuritis, peripheral neuritis, uveitis, and myelitis.

Several clinical features that are not common in adults are seen in children in the second phase of the disease, including hypertension, acalculous cholecystitis, pancreatitis, abdominal causalgia, and peripheral desquamation of a rash that may be associated with gangrene and cardiopulmonary arrest. Leptospirosis during pregnancy is associated with increased risk of fetal demise.⁷

Diagnosis

Diagnosis is based on culture of the organism or serologic proof of its existence. During the first phase, *Leptospira* may be readily isolated from the blood. Special media are required (eg, Fletcher's medium, Tween 80-albumin medium) for the organisms to be grown in vitro. The organisms may persist in the blood for 24 to 48 hours after the appearance of jaundice in icteric patients. At the end of the first phase of the illness, *Leptospira* are cleared from the blood; however, during the immune phase *Leptospira* may be cultured from the urine. The organisms may persist in the urine for up to 11 months despite treatment.

The laboratory diagnosis of leptospirosis is usually made by means of serologic tests. Two methods are currently used: a macroscopic slide agglutination test using killed antigen and a microscopic agglutination test using live antigen, which is more complicated but more sensitive. The microscopic agglutination test is used for determination of antibody titer and tentative identification of serotype. More recently, highly specific and sensitive enzyme-linked immunosorbent assay (ELISA), dot-ELISA, and gold immunoblot techniques of leptospiral IgM antibodies detection have been developed.⁸⁻¹³

Differential Diagnosis of Disease Caused by Rat Bites

The patient in this case report presents with liver dysfunction, azotemia, anemia, thrombocytopenia, clouded consciousness, and persistent fever, and he has a history of being bitten by a rat approximately 3 weeks prior to the onset of his symptoms. Rats and other rodents have been implicated in the transmission of a number of diseases. Important zoonoses that are linked to rats include rat-bite fever, endemic typhus, plague, Lassa fever, and leptospirosis.

Rat-bite fever. Rat-bite fever is caused by *Streptobacillus moniliformis* and *Spirillum minus* and is characterized by fever of abrupt onset, chills, maculopapular or petechial rash predominantly on the extremities, muscle pain, arthritis, and headache. Complications include pneumonia, localized abscesses in soft tissues, endocarditis, and pericarditis.

Endemic typhus. Endemic typhus is an acute febrile illness caused by *Rickettsia typhi* (*mooseri*) and transmitted to humans by fleas. Rats in whom the infection is inapparent are the natural hosts. The clinical illness is characterized by fever of 9 to 14 days, headache, maculopapular rash, and myalgia. Visceral complications are rare, and death usually does not occur.³

Plague. Plague is an enzootic infection of rodents and their fleas caused by *Yersinia pestis*. Human epidemics occur when the domestic rodent population (rats) becomes infected and their infected ectoparasites (fleas) spread the disease to humans. Plague usually presents as painful lymphadenitis (bubonic plague). Pneumonic, septicemic, meningial, and pharyngeal forms of plague are known but uncommon.

Lassa fever. Lassa fever is a viral disease that has been primarily reported in West Africa. *Mastomys natalensis*, a multimammate rat that is widespread in Africa, is the animal reservoir. Primary human cases result from food contamination with rodent urine. Signs and symptoms include fever, chills, headache, malaise, myalgias, pharyngitis, nontender lymphadenopathy, cough, hypotension, disseminated intravascular coagulation, and shock.

Leptospirosis. The term *leptospirosis* is applied to disease caused by all *Leptospira* regardless of serotype. Leptospirosis is thought to be the most widespread zoonoses in the world and is primarily a disease of teenage persons and young adults. The most common initial symptoms in patients with leptospirosis are meningitis, hepatitis, nephritis, fever of undetermined origin, influenza, Kawasaki syndrome, toxic shock syndrome, and Legionnaire's disease. Leptospirosis should be included in the list of differential diagnoses in any febrile patient with multisystem involvement.

Treatment and Prophylaxis

The treatment consists of specific antimicrobial therapy combined with supportive care. A variety of antibiotics including penicillin, streptomycin, the tetracycline congeners, erythromycin, and ampicillin have been used. Penicillin (1.5 million units intravenously every 6 hours)² is the drug of choice. In less severe cases, when the patient can tolerate oral therapy, doxycycline (100 mg twice daily), amoxicillin (500 mg four times daily), or ampicillin (500 to 750 mg four times daily) can be used.³

In contrast to earlier studies, recent evidence suggests that antibiotic therapy may be effective in severe leptospirosis even when treatment is delayed until relatively late in the course of the illness.¹³ Doxycycline (200 mg/day) is very effective for prophylactic therapy and should be considered for high-risk occupational groups with short-term exposure.² Preventive measures consist of vaccination of dogs and livestock, rodent control measures, and wearing protective clothing, boots, and gloves in order to reduce occupational exposure.

SUMMARY

The emergency physician should have a heightened awareness of this potentially fatal disease because early recognition and treatment may make the difference between complete recovery and a potentially fatal outcome.

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