Leptospirosis: A tropical disease presenting in the desert

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Abstract

Leptospirosis is likely the most common zoonotic disease worldwide and it is classically found in patients living in tropical and sub-tropical environments. It has recently emerged as an important travel-related infection, especially with adventure travelers exercising and exploring pooled bodies of water. Leptospirosis often manifests as a nonspecific febrile illness, but typical symptoms of leptospirosis include fever, headache, myalgias, jaundice, and conjunctival suffusion. Weil’s disease is the name given to the classic severe leptospirosis and is characterized by jaundice, renal failure, hemorrhage, and a high mortality rate. Due to the varying signs and symptoms, and the possibility of significant clinical consequences, it is important for clinicians to consider leptospirosis as a potential diagnosis. We describe a 46 year old previously healthy male who presents to the Emergency Department with fever, myalgias, and headache and recent travel history to Guam. The patient was found to have an acute kidney injury and was diagnosed with presumptive leptospirosis. He was started on correct antibiotic coverage upon admission and still required a 6 day hospital course before his renal function improved and he was discharged home. This case illustrates that physicians must have a high index of suspicion for leptospirosis in patients presenting with nonspecific febrile illness with recent travel to tropics or prolonged adventure activity in water.
Introduction
Leptospirosis may be the most common zoonotic disease worldwide.1 It is an under-reported disease without reliable incidence figures due to lack of awareness and systemic investigation. The World Health Organization’s (WHO’s) Leptospirosis Burden Epidemiology Group has estimated there are 873,000 cases worldwide annually causing 48,600 deaths.2 A 2008 study estimated annual incidence in the United States at 0.1 cases per million population.3 In 1995, the disease was removed from the United States list of nationally notifiable diseases. Hawaii is an exception, where the disease remains notifiable and the incidence rate is 12.9 cases per million.3

The organism causing Leptospirosis, *Leptospira interrogans*, thrives in warm, humid conditions; thus Leptospirosis is mainly seen in tropical locations. However, due to increased worldwide travel and average incubation time of 5 to 14 days, the disease can present in patients at any location.4,5 Some cases of Leptospirosis may be completely asymptomatic, and 90% of symptomatic cases are fairly mild and self-limited.1 Early disease presents with non-specific symptoms of fever, myalgias, and headache. Unfortunately, roughly 10% of symptomatic cases are severe and life-threatening.1 Jaundice, acute renal failure, thrombocytopenia, anemia, aseptic meningitis, and hemorrhage can be indications of severe leptospirosis cases.6

Diagnosis of leptospirosis relies on a detailed history and clinical suspicion, because the current testing methods do not yield results quickly enough to be clinically useful in an acutely ill patient.4 Studies have reported shortened duration of illness when appropriate antibiotic therapy was administered during the initial 2-4 days of illness.7 A retrospective case-control study has identified delay in antibiotic treatment greater than 2 days from start of symptoms as a risk factor for progression to severe leptospirosis.8 While early antibiotic treatment has proven to be beneficial to shortening course of disease, starting treatment later also has shown to reduce recovery periods and minimize sequelae.9 If risk factors are identified, then appropriately targeted interventions can successfully treat and prevent the disease. Therefore, physicians need to be aware of indications to consider Leptospirosis as a diagnosis, know how to treat the disease empirically, and know appropriate prophylactic measures.

Case Presentation
A 46 year old male presents to the emergency department (ED) in late October reporting four days of daily fevers, chills, myalgias, night sweats, and right-sided frontal and retroorbital headache and one day of right flank discomfort. He measured fevers up to 103 degrees Fahrenheit at home. He describes the flank pain as intermittent, dull, non-radiating, and 2/10 in severity. The patient also states that his urine has been dark lately. He denies neck stiffness, cough, chest pain, dyspnea, nausea, vomiting, diarrhea, bloody and black stools, ear pain, and weakness. The patient was seen at Urgent Care clinic prior to arrival and referred to ED when his bloodwork showed Creatinine of 2.1. Of note, the patient’s influenza swab was negative at clinic.

The patient reports that he flew to Phoenix the previous day from Guam. He works as a pilot for an international airline company and is based in Guam. The patient denies recent travel or work in any areas outside of Guam and United States. The patient is also actively involved in recreational sports. He enjoys mountain biking and trail running through jungles in Guam. He admits to lots of exposure to flooded water due to recent typhoons in that area. Also, patient states he has several recent mosquito bites. Patient notes that there are many feral dogs, pigs, and cats throughout Guam. He does not have any recent known exposure to sick individuals.

The patient denies significant past medical history. He does not take medications on a daily basis and denies known allergies. He has previous surgical history of vasectomy. The patient has had multiple
vaccinations including oral typhoid, hepatitis B and C, and influenza. The patient is married and has three
children. His family lives in Arizona. He denies history of smoking tobacco and recreational drug use. He
drinks alcohol occasionally. The patient’s father died of pancreatic cancer at age 71 and the patient’s
mother is alive at 68 and has Parkinson’s disease.

The patient’s 12-point review of systems is negative except for symptoms stated above.

On physical exam, presenting vitals are blood pressure 140/64, heart rate 90, respiratory rate 16, pulse
oximetry 98% on room air, and temperature 100.3°F. Head normocephalic, atraumatic. Eyes normal to
inspection with pupils equal, round and reactive to light. Extraocular muscles are intact, sclera was
anicteric, no conjunctiva suffusion. ENT shows dry mucous membranes, normal ears, and normal
posterior pharynx. Neck exam shows no jugular venous distention, no meningeal signs. Respiratory exam
breath sounds are normal and chest is nontender. There is no respiratory distress. Heart exam regular rate
and rhythm. No murmurs, gallops, or rubs present. Abdomen shows no distension, no masses palpated,
nontender to palpation. No costovertebral angle (CVA) tenderness to palpation. Spine processes and
paraspinal muscles nontender to palpation. Extremities no edema and 2+ distal pulses. No visualized
rashes over skin. Skin warm and dry. Neurological exam shows no focal motor deficits, speech is normal
and Glaesow coma scale is 15.

Initial laboratory studies included a complete blood count (CBC), comprehensive metabolic panel, and
urinalysis. CBC was within normal limits except for increased MCV of 94.2 fL (80-90), neutrophilia of
7.6 x 10^3/uL (2.25-7.00), and lymphopenia of 0.3 x 10^3/uL (0.9-4.0). The patient’s metabolic panel
showed decreased sodium of 131 mmol/L (136-133), decreased potassium of 3.3 mmol/L (3.5-5.0),
decreased chloride of 98 mmol/L (101-111), decreased calcium of 8.7 mg/dL (8.9-10.3), decreased
albumin of 2.9 g/dL (3.5-5.0), decreased protein of 5.9 g/dL (6.1-7.9), increased blood urea nitrogen
(BUN) of 30 mg/dL (8-20), increased creatinine of 2.13 mg/dL (0.7-1.2), increased glucose of 125 mg/dL
(65-99), increased aspartate transaminase (AST) of 174 IU/L (15-41), increased alanine transaminase
(ALT) of 179 IU/L (17-63), and increased alkaline phosphatase of 321 IU/L (38-126). Urine showed large
amount of blood and large amount of protein. Chest radiograph showed no acute cardiopulmonary
abnormalities. The patient was admitted for acute kidney injury with electrolyte abnormalities and
transaminitis. Serum creatinine kinase, blood cultures, abdominal ultrasound, and lumbar puncture with
cerebral spinal fluid (CSF) evaluation were test ordered on admission. The patient was started on empiric
coverage for possible bacterial infection with ceftriaxone and doxycycline. He was also given fluid
resuscitation with normal saline, and potassium replacement. On the second day of admission, the
patient’s platelets decreased to 120 x 10^3/uL (140-440), BUN and creatinine increased to 38 mg/dL (8-20)
and 4.24 mg/dL (0.7-1.2) respectively. The patient was seen by nephrology who ordered complement
levels, Anti-neutrophil cytoplasmic antibodies (ANCA), Anti–glomerular basement membrane (anti-
GBM), Anti-streptolysin O (ASO), serum protein electrophoresis (SPEP), and urine protein/creatinine
ratio to evaluate possible causes of intrinsic renal disease. The patient was also started on Solu-medrol by
the nephrologist. No gross abnormalities were found in any of the test results. A renal biopsy was
performed on the fourth day of admission and the results were negative for any significant
glomerulopathy. Infectious disease also saw the patient and ordered serologic testing for leptospirosis,
rickettsial disease, dengue fever, and typhoid. The patient was discharged on day 6, after his symptoms
and renal function improved. Serology studies were still pending at time of discharge. His discharge
diagnosis was presumed leptospirosis and he was given prescription for oral doxycycline.
Discussion

Leptospirosis is a zoonotic disease caused by pathogenic spirochetes of the genus Leptospira (Figure 1). It is a worldwide disease that presents in both tropical and temperate zones, though the incidence in the tropics is approximately 10 times higher than in temperate regions. In the United States, Hawaii consistently reports the most cases. The major reservoirs of the organisms are cattle, horses, canines and rodents. Leptospires burrow in the renal tubules of mammalian hosts and are then shed in the urine. The reason for higher incidence in tropical locations is due to longer survival of leptospires. Shed leptospires can survive for several months in the environment under moist conditions, mainly in the presence of warmth (above 22°C) and a neutral pH (pH 6.2–8.0). Humans are accidentally infected through contact with water, soil, or vegetation contaminated with mammalian urine. Organisms enter humans through skin abrasions or through the mucosal surface of the eye, mouth, nasopharynx, or esophagus (Figure 2).

In the tropics, endemic leptospirosis is mainly a disease of poverty. It is acquired through job-related exposure, such as subsistence farming, and living in rodent-infested, flood-prone urban slums. In temperate areas, infection rates are highest during summer and early autumn; while in the tropics, cases occur all year round with increased incidence during rainfall months. Recreational exposures are increasingly associated with outbreaks of leptospirosis. Specific activities linked with leptospirosis include freshwater swimming, rafting, kayaking, canoeing, fishing, hunting, and trail biking. Large outbreaks have been reported following a triathlon in Illinois in 1998, an endurance adventure race in Guam in 2002, and an endurance-length swamp race in Florida in 2005. Transmission between humans is very rare. Studies have also shown that severe leptospirosis with increased mortality occurs at a significantly higher rate in male patients than female patients, and those rates are not associated with different exposure risks or delays in treatment.

The appearance of symptoms typically begins with the abrupt onset of intense headache, fever, chills, and myalgias. Fever often exceeds 40°C (103°F) and is preceded by rigors. The clinical course of leptospirosis ranges from a mild acute febrile illness to life-threatening manifestations such as Weil’s disease, which consists of the triad of jaundice, acute renal failure, and hemorrhage. Also, Leptospirosis has been recognized as a significant cause of pulmonary hemorrhage syndrome worldwide. Conjunctival suffusion is an important but frequently overlooked clinical sign. Conjunctival suffusion is characterized by redness and edema, mostly on the palpebral conjunctiva (Figure 3). This is not a common finding in other infectious diseases, and its presence in a patient with a nonspecific febrile illness should raise the possibility of leptospirosis. Conjunctival suffusion and myalgias are considered pathognomonic of leptospirosis.

Laboratory findings with Leptospirosis are nonspecific. White blood cell counts are generally less than 10,000/uL, but can range from 3,000 to 26,000/uL. A left shift occurs in about two-thirds of patients. Hyponatremia is common in severe leptospirosis.

Approximately 40 percent of patients have minimal to moderate elevations of hepatic transaminases (usually <200 IU/L). Elevated creatine kinase is observed in approximately 50 percent of patients and may be a useful clue.

Chest radiography is also nonspecific. The images may demonstrate small nodular densities, which can progress to consolidation or a ground glass appearance.

Since clinical and laboratory findings are nonspecific, a high index of suspicion is required to make the diagnosis of leptospirosis based on epidemiologic exposure and clinical manifestations. Differential diagnosis of leptospirosis depends on clinical manifestation and area of acquisition of infection. The
differential may include influenza, malaria, dengue fever, viral hemorrhagic fevers, Hantavirus infection, Legionnaires’ disease, yellow fever, aseptic meningitis, sepsis, meningococcal disease, brucellosis, typhoid fever, rickettsial diseases, relapsing fever, viral hepatitis, and HIV.11

Serology is the most frequently used method to gain definitive diagnosis.2 However, results are dependent on timing of samples taken and samples need to be collected both during acute and convalescent stages of disease for comparison.16 Microscopic agglutination test (MAT) is the gold standard for definitive diagnosis. It requires live organisms, expert training, and is only performed by reference laboratories such as United States Centers for Disease Control and Prevention (CDC).2 Due to technicalities of MAT testing, a serologic assay is usually performed first and then, if positive, serum can be sent for MAT to CDC. Culture of leptospires in clinical specimens takes several weeks and is of low sensitivity.11 Research is currently being directed at developing more accurate rapid diagnostic tests.17

In the setting of moderate or high clinical suspicion for leptospirosis, administration of empiric treatment is appropriate to shorten duration of illness and prevent progression to severe disease. The recommended treatment for mild leptospirosis is oral doxycycline or oral azithromycin. The recommended therapy for treatment of patients with severe leptospirosis is parenteral penicillin, doxycycline, or third-generation cephalosporins.18 In severe cases, supportive care with dialysis, ventilation, and transfusions may be necessary. There is currently insufficient evidence to recommend routine use of corticosteroids in treatment.18

Patients with leptospirosis would be expected to have increased sympathetic activity due to the disease process. Osteopathic treatment for such infectious processes should aimed at decreasing sympathetic activity or increasing parasympathetic activity. Rib raising is a potential treatment technique that can mobilize ribs for improved respiration, produce long lasting sympathetic inhibition, and improve lymphatic return. After sympathetic tone has normalized, thoracic pump is a treatment technique that can also improve lymphatic return. Fever is an indication for treatment with both rib raising and thoracic pump.19

No human vaccine is available. Prevention measures include avoiding potential sources of infection, administration of antibiotic prophylaxis for individuals at high risk of exposure, and animal vaccination.19 A study evaluating doxycycline prophylaxis in US soldiers training in Panama found significantly less cases of leptospirosis in soldiers who received prophylaxis compared to the placebo group.20 Pretravel risk assessment for leptospirosis should evaluate information about high-risk activities for acquisition of infection and travel destination should be considered prior to administering prophylaxis.11

In summary, this case serves to remind of the importance of communication with patients and obtaining a thorough travel and exposure history. Our patient presented to an Arizona hospital with non-specific symptoms of febrile illness. His diagnosis was found to be presumed leptospirosis, an infectious disease traditionally associated with tropical climates with heavy rainfall, environments opposite that of Arizona. This diagnosis and subsequent effective treatment would not have been realized without a complete patient history.

Osteopathic philosophy emphasizes preventative medicine and comprehensive patient care. Communication is one of our simplest yet most valuable tools. Collecting patients’ travel history can be a means of early detection of disease.21 Many infections associated with travel to endemic areas can be prevented with prophylaxis or controlled with early treatment intervention.
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Figure 1: Scanning electron micrograph of Leptospira interrogans. Original magnification, x17,000. Reprinted from Goldman’s Cecil Medicine, 24th ed.⁶
Figure 2: Transmission of Leptospirosis.
Figure 3: Conjunctival suffusion. Reprinted from Goldman's Cecil Medicine, 24th ed.\textsuperscript{6}