Danger in Paradise

<div style="text-align:right">**17**</div>

Margaret Newman

A 31-year-old man became sick on the last day of his 3-week-long trip to Southeast Asia with sudden onset of fever, arthralgia, and headache. He attributed his symptoms to exhaustion and boarded a plane back to the United States (USA), but the symptoms persisted. The following day he also had several loose, non-bloody stools which were self-limited. Three days after departing Hong Kong, he presented to his Student Health Center for evaluation. Prior to his trip, he had not visited a travel clinic or received malaria prophylaxis.

The patient was originally from Colombia, but he had moved to the USA for his undergraduate and graduate education. He had not been to South America for more than 2 years. His trip to Southeast Asia included 10 days in Thailand, 4 days in Cambodia, 6 days in Laos, and 1 day in Hong Kong. His American girlfriend accompanied him on the trip and did not develop similar symptoms. While on vacation, they rode elephants, hiked through a jungle, and slept on a beach. They also swam in a waterfall and encountered local monkeys, though he did not recall any bites or scratches from a monkey. He drank mostly bottled water, but he ate local sushi and drank fruit juices purchased from street vendors. He denied any local sexual contacts. He used insect repellent intermittently during his trip but suffered many mosquito bites. He felt well throughout the majority of the trip.

The patient's past medical history was unremarkable. He was taking no prescribed medications, although he did take a few doses of acetaminophen and ibuprofen for the joint pains over the previous 3 days. He was enrolled in business school and lived in Chicago. He did not use drugs or smoke cigarettes. In addition to the fever, headache, and arthralgia, the patient also complained of appetite loss and fatigue. He was not having any abdominal pain or vomiting. He had no vision changes or neck pain.

On presentation, the patient was found to be febrile to 102 °F, mildly tachycardic at 99 beats per minute, normotensive at 115/75 mmHg, and had a respiratory rate of 16 breaths per minute. He had no enlarged joints and no findings of synovitis, but the provider incidentally noted a faintly erythematous, patchy rash over both anterior knees (see Fig. 17.1). The patient had not previously noted the rash as it was not tender or pruritic. His eyes were notable for mild scleral injection bilaterally. There was no appreciable lymphadenopathy, and the oropharynx was clear. The abdomen was soft and non-tender without enlargement of spleen or liver.

An infectious diseases consultation service was requested by the Student Health Clinic

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provider. The differential diagnosis for a returning traveler from Southeast Asia with a febrile illness of a relatively short incubation (maximum 21 days) is summarized in Table 17.1. It includes mosquito-borne infections (malaria, dengue fever, Zika virus, chikungunya virus, and Japanese encephalitis), mite-borne scrub typhus (*Orientia tsutsugamushi*), *Salmonella typhi* (typhoid fever), brucellosis, leptospirosis, acute viral hepatitis (especially A or E), and visceral leishmaniasis. Acute retroviral syndrome (human

Fig. 17.1 Rash on the anterior right knee at presentation

Table 17.1 Differential diagnosis for a traveler returning from Southeast Asia with fever, myalgia, arthralgia, and rash with a relatively short incubation period (<21 days)

Dengue fever (flavivirus)
Zika virus (flavivirus)
Chikungunya virus and other uncommon alphaviruses
Scrub typhus (*Orientia tsutsugamushi*)
Leptospirosis (*Leptospira* spp.)
Salmonella typhi (typhoid fever)
Acute human immunodeficiency virus (HIV) infection
Influenza
Flinders Island spotted fever (*Rickettsia honei*)
Secondary syphilis (*Treponema pallidum*)
Mononucleosis (Epstein-Barr virus)
Parvovirus
Measles
Rubeola
Hepatitis A
Hepatitis E
Japanese encephalitis infection (flavivirus)
Malaria (usually no rash)

immunodeficiency virus [HIV]) and secondary syphilis would usually be in the differential diagnosis as they may cause similar symptoms, but these diagnoses were less likely in view of the patient's reported sexual history. More commonly encountered viral causes of fever and arthralgias, such as seasonal influenza, mononucleosis, and parvovirus, were also considered. Other rickettsial diseases (such as Flinders Island spotted fever in Southeast Asia) may present with similar symptoms, but a prominent diffuse rash would be expected. Tularemia and ehrlichiosis can also cause fever, arthralgia, and rash, but these diseases are not endemic in either Southeast Asia or Chicago.

Given the prolonged processing time required for serological studies for several of these infectious syndromes, it was recommended that the patient have basic electrolyte and hematologic laboratory studies, with hospital admission if they were abnormal. A malaria smear was negative, but the creatinine was significantly elevated to 2.1 mg/dL (normal range, 0.5–1.4 mg/dL) from a baseline value 0.9 mg/dL. The patient was admitted to the hospital for further evaluation. Liver function tests were slightly elevated, with alanine aminotransferase (ALT) of 49 U/L (8–35 U/L) and aspartate aminotransferase (AST) of 45 U/L (8–37 U/L). Antibody tests for dengue virus, chikungunya virus, Zika virus, and leptospirosis were sent to the US Centers for Disease Control and Prevention (CDC) for processing. A fourth-generation HIV screening test was nonreactive. A respiratory viral panel polymerase chain reaction (PCR) test was negative. Repeat malaria smears were also negative. Table 17.2 shows a complete list of the patient's laboratory test results. The acute kidney injury resolved after 12 hours of intravenous fluids, liver function tests normalized the following day, and the patient's symptoms improved. At this point he was discharged from the hospital with a 7-day course of empiric oral doxycycline while the infectious diseases serologies sent to the CDC were still pending. Several days later, the *Leptospira* IgM antibody test came back positive. Antibody tests for dengue, chikungunya, and Zika viruses were negative.

Table 17.2 Laboratory values

Test name	Patient value	Reference range
White blood cell count	8100/μL	3500–11,000/μL
Hemoglobin	14.6 g/dL	13.5–17.5 g/dL
Hematocrit	42%	41–53%
Mean corpuscular volume (MCV)	87.8 fL	81–99 fL
Platelet	126,000/μL	150,000–450,000/μL
Neutrophils	77%	39–75%
Lymphocytes	16%	16–47%
Monocytes	7%	4–12%
Eosinophils	0%	0–7%
Basophils	0%	0–2%
Sodium	138 mmol/L	134–149 mmol/L
Chloride	97 mmol/L	95–108 mmol/L
Blood urea nitrogen (BUN)	23 mg/dL	7–20 mg/dL
Glucose	110 mg/dL	60–109 mg/dL
Potassium	3.6 mmol/L	3.4–5.0 mmol/L
Carbon dioxide	21 mmol/L	23–30 mmol/L
Creatinine	2.1 mg/dL	0.4–1.4 mg/dL
Total bilirubin	0.4 mg/dL	0.1–1.0 mg/dL
Total protein	7.5 g/dL	6.0–8.3 g/dL
Albumin	4.2 g/dL	3.5–5.0 g/dL
Alkaline phosphatase	82 U/L	30–120 U/L
Aspartate aminotransferase	45 U/L	8–37 U/L
Alanine aminotransferase	49 U/L	8–35 U/L
Lactic acid	0.8 mmol/L	0.7–2.1 mmol/L
Urinalysis	Color yellow	Specific gravity 1.016–1.022
	Clarity turbid	pH 5.0–9.0
	Specific gravity 1.016	Urobilinogen 0.1–1.0 g/dL
	pH 5.0	
	Leukocyte esterase negative	
	Nitrites negative	
	Protein 2+	
	Blood 3+	
	Glucose 1+	
	Ketones negative	
	Bilirubin negative	
	Urobilinogen 0.2 g/dL	
Respiratory viral panel[a]	Negative	Negative
Malaria smear (Giemsa), thick and thin smears	Negative	Negative
Dengue fever Ab, IgG	Negative	Negative
Dengue fever Ab, IgM	Negative	Negative
Chikungunya Ab, IgG	Negative	Negative
Chikungunya Ab, IgM	Negative	Negative
Leptospira Ab, IgM	Positive	Negative
HIV 1/2 antibody/antigen screen	Nonreactive	Nonreactive
Blood cultures	Negative	Negative

[a]The respiratory viral panel tests by the polymerase chain reaction for the following pathogens: adenovirus, coronavirus 229E, coronavirus HKU, coronavirus NL63, coronavirus C43, human metapneumovirus, rhinovirus/enterovirus, H1 2009 subtype of influenza A, H1 subtype of influenza A, H3 subtype of influenza A, influenza A, influenza B, parainfluenza 1–4, respiratory syncytial virus (RSV), *Bordetella pertussis*, *Chamydophila pneumoniae*, *and Mycoplasma pneumoniae*

17.1   Leptospirosis

Leptospira is a zoonotic spirochete bacterial genus that frequently contaminates soil or surface water. It was first discovered in 1883 in sewer workers, as the pathogen is commonly spread by rodent urine in stagnant water. The clinical syndrome of renal failure, jaundice, and thrombocytopenia was described by Adolf Weil (1848–1916) in 1886 [1]. The *Leptospira* spirochete resides in the renal tubules of chronically infected animal hosts who do not display symptoms of illness, and bacteria are shed in the urine. They survive in surface fresh water for months to years. Rodents often spread disease in urban areas, but dogs and livestock can also be infected.

Humans may be infected via direct contact with animals or, more often, indirectly through contact with water or soil contaminated by the urine of infected animals, such as when skin abrasions or mucous membranes are exposed to contaminated water [2]. Leptospirosis is an occupational zoonosis more common in persons who handle animals (veterinarians, workers on dairy farms, abattoir workers, butchers, hunters, animal and dog handlers) or are exposed to contaminated wet soil or surface water (e.g., rice farming). Recreational- and sport-related exposures have become more prevalent.

Human disease is most prevalent in tropical regions, especially where precipitation is frequent, and large epidemics may occur after heavy rainfalls and floods. Leptospirosis is present in both tropical and temperate regions of the world including the USA. The World Health Organization (WHO) estimates the rate of leptospirosis at 0.1–0.2 cases per 100,000 people in temperate climates and 100/100,000 in tropical climates [3].

Leptospirosis in humans can present with a wide spectrum of severity, from a mild febrile illness to severe, life-threatening illness associated with multi-organ dysfunction.

Uncomplicated anicteric leptospirosis is by far the most common presentation. In the early septicemic phase, patients have acute onset of high fever, chills, headache, nausea, vomiting, and the very intense myalgias of the calf, paraspinal, and abdominal muscles that may often suggest the diagnosis. Conjunctival suffusions (erythema without discharge) are another diagnostic clue often identified on day 3 or 4. When seen, the rash is usually transient and may be urticarial, macular, maculopapular, erythematous, or purpuric. Labs may show leukocytosis or a normal white count with a left shift, thrombocytopenia, mild anemia, mild hyperbilirubinemia, and in some a mildly elevated creatinine.

Fever may recur after a remission of 3–4 days, producing a biphasic illness. In the immune phase, patients may develop recurrent fever and constitutional symptoms, such as aseptic meningitis, eye involvement, and peripheral neuropathy. Some patients may go on to develop chronic or recurrent uveitis.

Icteric leptospirosis (Weil disease) occurs in less than 10% of diagnosed cases. It may appear to be severe from the onset, or it may develop as a biphasic illness that initially appeared to be mild. Weil disease is a syndrome of high fever, jaundice with very high bilirubin but only moderately elevated transaminases (in the 100s), non-oliguric acute renal failure, and rarely thrombocytopenia and disseminated intravascular coagulation leading to cutaneous, gastrointestinal, and pulmonary hemorrhage. When bleeding is prominent, hemorrhagic fever with renal syndrome due to hantaviruses is in the differential diagnosis. Some patients with severe leptospirosis have isolated pulmonary involvement with hemorrhage and acute respiratory distress syndrome (ARDS).

It is estimated that about 50,000 cases of leptospirosis are fatal worldwide each year [4]. Patients with suspected leptospirosis should be monitored closely for renal or liver injury. Earlier treatment with appropriate antibiotics is associated with decreased risk of severe illness and complications. In a 2015 review of mortality trends of leptospirosis, there was a significant correlation between presence of jaundice and mortality [4].

Increased age and renal dysfunction were also associated with increased risk of death.

Diagnosis of leptospirosis is complicated by the lack of a cost-effective and simple diagnostic test. Of existing diagnostic tests, the microcapsule agglutination test (MAT) is considered to be the gold standard. However, the test requires the maintenance of live *Leptospira* cultures and technical expertise, and may take several days to result [5], which is often not practical in areas of the world most affected by leptospirosis. In addition, the MAT does not differentiate between past infection and active infection or between different serovars of *Leptospira*. The lateral flow test and latex agglutination test are older immunoassays routinely used to detect *Leptospira*-specific antibodies, but they are less specific than the MAT [5]. PCR-based tests have also been developed to help distinguish between different serovars of *Leptospira*, but they are similarly infeasible in countries with limited resources.

Prevention of leptospirosis with vaccination is limited by the genetic variations with a large number of species that cause human disease in the world, making it unlikely that a single vaccine will be effective. Vaccination for pets is available in the USA, but it does not prevent the spread of the pathogen to humans. Prophylactic medication for travelers was proven to be effective in a study of US soldiers stationed in Panama. Of the 940 soldiers enrolled in the blinded study, 0.2% of those who took 200 mg of doxycycline weekly developed leptospirosis, compared with 4.2% in the placebo group [6]. Similar studies have been attempted in endemic regions without a statistically significant difference between placebo and prophylaxis groups. The WHO officially recommends that travelers who are going to a region affected by natural disasters and likely contaminated fresh water receive doxycycline prophylaxis [1].

Treatment of leptospirosis is primarily doxycycline 200 mg daily for 7 days [7]. Studies of *Leptospira* isolates from several of the most commonly affected regions in the world identified no instances of doxycycline or tetracycline resistance, although higher MICs were noted with *Leptospira* strains from Egypt. *Leptospira* is susceptible in vitro to most penicillins, macrolides, cephalosporins, and fluoroquinolones. Severe leptospirosis often is treated with intravenous penicillin or a third-generation cephalosporin, but treatment may be complicated by the Jarisch-Herxheimer reaction, similar to that associated with other spirochete infections including syphilis and relapsing fever [7]. Studies of serologic biomarkers in leptospirosis patients have shown that cytokines such as TNFα, IL-6, IL-8, and PTX3 may be positively correlated with mortality from the infection [8], but the use of these prognostic tests is not yet validated.

Key Points/Pearls
- Consider leptospirosis as a potential diagnosis in a returning traveler with fever, myalgia (calf, spinal, and abdominal muscles), arthralgia, conjunctival suffusions, and sometimes a rash, diarrhea, and/or jaundice, the CBC may show leukocytosis or a left shift, thrombocytopenia; hyperbilirubinemia without significant transaminitis is present in most patients.
- Leptospirosis is a zoonotic pathogen that poses a significant health risk to native populations of and travelers to endemic regions and is contracted by exposure of mucous membranes or skin breaks indirectly to freshwater contaminated by animal urine or directly to infected animals (especially rodents, dogs, and cattle).
- Severe jaundice and acute renal injury are poor prognostic indicators of outcome in severe leptospirosis (Weil disease), and bleeding may be prominent (skin, GI, and lungs).
- Pulmonary hemorrhage and ARDS are seen in severe cases, sometimes without icterus.
- MAT is the reference standard test for diagnosis of leptospirosis; testing capabilities for leptospirosis are limited in endemic regions.
- Leptospirosis can be prevented in travelers by avoiding exposure to contaminated freshwater

and taking doxycycline weekly when this is unavoidable (such as after flooding).

- Empiric treatment of mild leptospirosis is a course of oral doxycycline.
- Severe leptospirosis should be treated in hospital with intravenous penicillin or a cephalosporin.

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