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61-Year-Old Man With Bilateral Leg Pain, Abdominal Pain, and Thrombocytopenia

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See end of article for correct answers to questions.

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A 61-year-old man presented to the emergency department with a 10-day history of nausea, vomiting, subjective fevers and chills, body aches, decreased urine output, and periumbilical abdominal pain. He denied diarrhea, chest pain, dyspnea, or urinary symptoms. Ten days earlier, he had returned from a 9-day trip to Jamaica with his wife, during which time she experienced 5 days of diarrhea, vomiting, and fevers but had since recovered. His medical history was notable for paroxysmal atrial fibrillation and gastroesophageal reflux disease. Current medications included 81-mg once-daily aspirin and 25-mg twice-daily metoprolol tartrate. He was an automobile mechanic and an ex-smoker who denied alcohol or recreational drug use.

Emergency department assessment revealed an ill-appearing male with normal blood pressure, heart rate, respiration rate, and room air oxygenation. Physical examination revealed generalized abdominal tenderness with no guarding, rebound tenderness, or positive Murphy sign. Cardiovascular examination revealed a normal rate and rhythm with no murmurs. Lung fields were clear. There was no rash, jaundice, or adenopathy. Laboratory studies revealed the following (reference ranges provided parenthetically): hemoglobin 18.1 g/dL (13.5 to 17.5 g/dL), white blood count (WBC) 13.8 x 10^9/L (3.5 to 10.5 x 10^9/L), platelet count 146 x 10^9/L (150 to 450 x 10^9/L), aspartate aminotransferase (AST) 49 U/L (8 to 48 U/L), total bilirubin 1.2 mg/dL (0.1 to 1.0 mg/dL), and creatinine 1.1 mg/dL (0.6 to 1.4 mg/dL). Abdominal ultrasound and computed tomography (CT) scan results were unremarkable. The patient was discharged home with a prescription for ondansetron.

Two days later the patient returned to the emergency department with new bilateral leg pain, anorexia, dark urine, and ongoing nausea and vomiting. He denied diarrhea, sore throat, chest pain, or arm pain. He was afebrile, and his blood pressure was 96/69 mm Hg; heart rate varied from 77 to 158 beats per minute, with normal respiratory rate and room air oxygen saturation. Physical examination revealed jaundice, scleral icterus, and no skin rash. Cardiac examination revealed an irregularly irregular heart rate with no murmurs. Lungs were clear, and the abdomen was diffusely tender. He had tenderness to palpation of the bilateral proximal thighs and calves.

Laboratory analysis revealed: hemoglobin 14.8 g/dL (13.5 to 17.5 g/dL), WBC 11.8 x 10^9/L (3.5 to 10.5 x 10^9/L), platelet count 33 x 10^9/L (150 to 450 x 10^9/L), C-reactive protein (CRP) 215.8 mg/L (0.0 to 4.9 mg/L), total bilirubin 6.7 mg/dL (0.1 to 1.0 mg/dL), AST 152 U/L (8 to 48 U/L), alanine aminotransferase (ALT) 69 (0 to 49 U/L), alkaline phosphatase 64 U/L (38 to 128 U/L), creatinine 3.0 mg/dL (0.6 to 1.4 mg/dL), troponin I 0.102 ng/L (0.012 to 0.034 ng/L), creatine kinase (CK) of 4671 U/L (43 to 310 U/L), and lactate dehydrogenase of 733 U/L (313 to 618 U/L). Fecal occult blood test result was negative, and urinalysis was notable for 21 to 30 red blood cells per high-powered field (hpf) (</hpf), large hemoglobin (negative), and glucose 631 mg/dL (0 to 15 mg/dL).

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Electrocardiogram revealed atrial fibrillation with rapid ventricular response that was converted to sinus rhythm with intravenous (IV) diltiazem.

1. **What would be the next best test for this patient?**
   a) HIV screening antibody/antigen testing
   b) Antibodies against platelet factor 4 (PF4)
   c) Peripheral blood smear
   d) Malaria blood smear
   e) Complement C3 and C4

Testing for HIV should be considered, as thrombocytopenia may be seen with HIV infection. However, a precipitous platelet drop over 2 days is not characteristic of HIV. PF4 is a protein stored in platelet alpha granules that is released during platelet activation. Antibodies against PF4 complexed with heparin are the main driver of heparin-induced thrombocytopenia (HIT) and should be tested when HIT is suspected. However, our patient had not received any recent heparin therapy. Peripheral blood smear will help determine if the patient has true thrombocytopenia, or if this is a spurious result, and to assess for other cell dyscrasias. In addition, the patient's presentation is concerning for possible hemolysis or thrombotic thrombocytopenic purpura (TTP), which should be first assessed with a peripheral smear. There is no malaria in Jamaica, so a malaria smear should not be performed. Complement testing is appropriate in adults for whom complement-mediated thrombotic microangiopathy is suspected, although a peripheral smear should initially be performed before complement testing to confirm hemolysis.

Our patient's peripheral smear was notable for thrombocytopenia with no other cell abnormalities or signs of hemolysis. Haptoglobin was elevated at 260 mg/dL (30 to 200 mg/dL), which made hemolysis unlikely. It was thought that the thrombocytopenia was caused by an underlying infection.

Additional Jamaica trip details revealed that the patient only ate at his resort. He denied eating undercooked meat, unpeeled fruit, or street-vendor food, and he only drank potable water. The patient and his wife went cliff jumping a few times into a freshwater pool in a local river.

2. **What is this patient's most likely diagnosis?**
   a) Dengue fever (DF)
   b) Typhoid fever (TF)
   c) Malaria
   d) Leptospirosis
   e) Chikungunya fever (CF)

Dengue is an arbovirus transmitted by the bite of an *Aedes* genus of mosquito that is endemic in tropical and subtropical regions throughout the world, with an incubation of 3 to 14 days, and symptom onset typically between 4 and 7 days. It is an acute febrile illness that includes at least 2 of the following: headache, retro-orbital or ocular pain, myalgia or bone pain, arthralgia, rash, hemorrhagic manifestations, or leukopenia.[1] Dengue hemorrhagic fever (DHF) may be associated with thrombocytopenia, pleural effusions, or ascites in addition to hemorrhagic manifestations such as mucosal bleeding, petechiae, purpura, hematemesis, or melena. Dengue shock syndrome may be associated with severe abdominal pain, nausea, and emesis as well as circulatory collapse. Dengue infections are not generally associated with marked hyperbilirubinemia, rhabdomyolysis.

Typhoid fever is an infection caused by ingestion of *Salmonella enterica* serotype Typhi or other Salmonella serotypes and is acquired by the ingestion of contaminated food or water; it is highly prevalent in Asia and southern Africa, but also found in Central and South America and the Caribbean. Typhoid fever typically presents within 5 to 21 days of exposure with fevers, abdominal pain, diarrhea (50% to 78%) or constipation (30%), and "rose spots," which are faint salmon-colored macules on the trunk and abdomen. In the third week of illness, hepatosplenomegaly, intestinal bleeding, and bowel perforation may occur. Laboratory analysis typically reveals abnormal liver

function tests and elevated CRP. Diagnosis may be made by culture of the blood (50% to 70% sensitivity) or bone marrow (>90% sensitive), although the latter is rarely indicated in clinical practice.[2] Thrombocytopenia and rhabdomyolysis are not characteristic of TF.

Malaria is a parasite transmitted by the bite of *Anopheles* mosquitos in parts of Africa, Southeast Asia, the Caribbean, and Central and South America. Malaria incubation period ranges from 12 to 35 days. Initial clinical manifestations may include fever, chills, malaise, cough, anorexia, nausea, vomiting, abdominal pain, arthralgias, and myalgias. Severe malaria may be associated with renal or hepatic failure, thrombocytopenia, and elevated liver enzymes. Malaria is not endemic in Jamaica.

Leptospirosis is an infection that is caused by bacteria in the genus *Leptospira* that infects a wide variety of animals including dogs, rodents, and farm animals, which may act as reservoirs that shed the organism into the freshwater environment in their urine. Humans become infected when the organism in contaminated water or soil enters microabrasions of the skin, mucous membranes, or the conjunctiva; handling of infected animals; or with the ingestion of contaminated food or water.[3] Leptospirosis is widespread throughout the tropics. After an incubation period of 2 to 26 days, clinical symptoms of the bacteremia phase of disease may include fevers, myalgias, headaches, mild gastrointestinal symptoms, and conjunctival suffusion. Other symptoms may include cough, nausea, vomiting, and diarrhea. The second, or immune phase of the disease occurs, in 5% to 15% of patients and may be associated with hepatic and renal failure, pulmonary hemorrhage, acute respiratory distress syndrome, myocarditis, and rhabdomyolysis. Laboratory abnormalities during this phase may include thrombocytopenia, proteinuria, elevated CK, moderate elevations in liver aminotransferases, marked hyperbilirubinemia, respiratory failure, and acute kidney injury.[3] Leptospirosis is most consistent with our patient's presentation and recent freshwater exposure in Jamaica.

Chikungunya is a virus transmitted by the bite of the *Aedes* genus of mosquito that was first identified in Tanzania in 1952, and for 50 years was associated with occasional outbreaks in Africa and Asia. Since 2004, chikungunya has spread rapidly throughout the tropics and has now been identified in many countries throughout Asia, Africa, Europe, the Caribbean, and the Americas. Onset of illness occurs 4 to 8 days following the bite on an infected mosquito and is characterized by fever, malaise, and severe polyarthralgias that may persist for months.[4] Other common signs and symptoms include myalgias, joint swelling, headache, nausea, fatigue, and rash. Liver enzyme abnormalities and rhabdomyolysis are not typical of chikungunya.

3. **What would be the next best test to help establish the diagnosis?**
   a) Bacterial urine culture
   b) Bacterial blood culture
   c) Darkfield examination of the urine
   d) *Leptospira* polymerase chain reaction (PCR) of the blood
   e) Leptospira IgM-enzyme linked immunosorbent assay (ELISA)

Culture of the urine or blood for *Leptospira* is laborious and time consuming and is only performed at reference laboratories and the Centers for Disease Control (CDC). In the bacteremic phase of leptospirosis (first 10 days), the leptospires may be cultured from blood and after 10 days of illness from the urine but is insensitive (5% to 50%). Darkfield examination of the urine is insensitive (40.2%) and nonspecific (61.5%).[3] *Leptospira* PCR of whole blood is available at the CDC and some commercial laboratories and is highly sensitive (100%) and specific (93%) but may be negative beyond the bacteremic phase of infection, as in our patient. The Karius test (https://kariusdx.com) has been reported to detect *Leptospira* microbial cell-free DNA circulating in the bloodstream by the manufacturer and in a *Leptospira* case report.[5] Serologic testing is the most widely used leptospirosis diagnostic test, although it is

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not helpful for those living in endemic regions. In naïve patients, antibodies appear 5 to 7 days following the onset of illness. *Leptospira* IgM ELISA is a good screening serology for this patient, as it is widely available and has a >90% sensitivity and 88% to 95% specificity. The *Leptospira* microscopic agglutination test (MAT) is the confirmatory serologic test, which may be performed at the CDC. Early negative MAT serologic screening should be repeated with paired convalescent samples collected at least 7 to 14 days apart, with a 4-fold rise in titer supporting a leptospirosis diagnosis.

Our patient was found to have a positive screening *Leptospira* IgM ELISA and negative Hepatitis A/B/C, dengue and chikungunya serologies.

4. **What is the best treatment for our patient?**
   a) Supportive care
   b) Oral doxycycline for 7 days
   c) Intravenous ceftriaxone for 7 days
   d) Intravenous methylprednisolone
   e) Plasmapheresis

Although leptospirosis is typically self-limiting, leptospirosis with multi-organ involvement should be treated with antibiotics and not supportive care alone because of the mortality risk of untreated leptospirosis.[6] Oral doxycycline is the antibiotic of choice for mild cases of leptospirosis, with ampicillin or amoxicillin alternatives for pregnancy and children younger than 8 years of age.[3,7] Treatment with IV antibiotics, such as a penicillin G, ampicillin, or ceftriaxone, is recommended for severe leptospirosis.[3] A Jarisch-Herxheimer reaction may occur following initiation of penicillin therapy for leptospirosis. This is a self-limiting acute inflammatory response to clearance of spirochetes from the circulation and is characterized by fever, rigors, and hypotension. Neither steroids nor plasmapheresis is indicated for the treatment of severe leptospirosis.

Our patient was treated with once daily IV ceftriaxone for 7 days.

5. **Which factor is associated with the lowest risk of mortality for severe leptospirosis?**
   a) Age <15 years
   b) Weil disease (hyperbilirubinemia plus renal failure)
   c) Pulmonary hemorrhage
   d) Oliguric renal failure
   e) Conjugated bilirubin >20 mg/dL

The mean case fatality rate of leptospirosis in 35 studies reporting mortality rate was 6.85% (95% confidence interval [CI], 5.66% to 8.03%) with an increased risk of death in adults >60 years and male patients, whereas death was rare in patients younger than than 15 years of age.[8] Patients with the more severe form of leptospirosis, also known as Weil disease (jaundice, renal failure), have a case fatality rate of 5% to 15%.[7] Severe pulmonary involvement has been shown to be a poor prognostic factor when associated with alveolar hemorrhage and acute respiratory distress syndrome (ARDS).[9] Oliguric renal failure is a significant predictor of death, although it often resolves even if dialysis is required.[7] Our patient underwent a brief course of hemodialysis but had full renal recovery by the time of hospital discharge 11 days after presentation. Leptospirosis can cause microscopic bile leaks, resulting in acute jaundice and extremely high serum conjugated bilirubin concentrations. However, liver function generally recovers, as was true for our patient who had a peak total bilirubin of 46 mg/dL with complete liver function recovery in 8 weeks.

DISCUSSION

Leptospirosis is the most widespread zoonotic infection in the world.[8] Leptospirosis is caused by Leptospira species, which are transmitted to humans by exposure to freshwater bodies or environments contaminated with the urine of infected mammals or by direct exposure to infected animals.[3] The portal of entry is through ingestion or via direct contact with openings in the skin, mucosal surfaces, or conjunctiva, although infection may occur through intact skin.

The incidence of leptospirosis is highest in tropical regions where there are an estimated 1.03 million human infections and 58,900 deaths per year, although this disease is likely under-reported.[8] This disease disproportionately affects urban slum residents and rural subsistence farmers in the tropics. In the United States, there were 100 to 200 cases reported annually to the CDC from 2014 to 2018. Most US cases are reported in Puerto Rico and Hawaii, although there were cases reported from the mainland following hurricanes Irma and Maria (2017) and among participants of freshwater sports. Leptospirosis was the third most common bacterial cause of serious acute febrile infection in returned travelers in a recent report and was associated with freshwater activities (swimming, rafting) and largely seen in men and tourist travel to Southeast Asia.[10]

Leptospirosis clinical presentation can be nonspecific or mild in 90% of cases. Mean leptospirosis incubation is 10 days (range 5 to 14 days) and may present as a biphasic illness. The primary or bacteremic phase is associated with fever, headache and myalgias, nausea, vomiting, abdominal pain, and conjunctival suffusion and lasts for 5 to 7 days. The headache may be severe with retro-orbital pain, which may mimic DF. The immune or icteric phase may last 4 to 30 days and coincides with clearance of the bacteremia; it is characterized by fevers and multisystem involvement including elevated liver enzymes (primarily conjugated bilirubin with moderate transaminase elevation), acute renal failure, pulmonary involvement including hemoptysis, respiratory failure and ARDS, and aseptic meningitis. Weil disease, which is characterized by impaired hepatic and renal function, occurs in 5% to 10% of cases.[3] Left untreated, severe leptospirosis may progress to life-threatening complications including hepatic and renal failure, severe pulmonary hemorrhagic syndrome, myocarditis, and rhabdomyolysis. Mild leptospirosis may be treated with oral antibiotics such as doxycycline, penicillin, or amoxicillin. Severe leptospirosis should be treated with IV antibiotics such as penicillin G, ampicillin, or ceftriaxone.[3] In high-income countries, most symptomatic leptospirosis cases will respond to timely antibiotic treatment, resulting in complete resolution of disease without sequelae, as with our patient.[10] Immunization of agricultural and companion animals with killed vaccines is widely practiced in high-income countries to prevent disease and reduce human exposure. Human *Leptospira* immunization is not widely practiced. Doxycycline, taken as 200 mg once weekly, has been shown to be effective prophylaxis for high-risk overseas travelers and could be considered in endemic regions in the tropics following heavy rainfalls.[11]

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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CORRECT ANSWERS: 1. c. 2. d. 3. e. 4. c. 5. a