CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 31-2024: A 37-Year-Old Man with Fever, Myalgia, Jaundice, and Respiratory Failure

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PRESENTATION OF CASE

Dr. Danielle C. Crabtree (Medicine): A 37-year-old man was admitted to this hospital because of fever, myalgia, jaundice, and hypoxemia.

The patient had been healthy until 9 days before this admission, when malaise, fatigue, and generalized weakness developed. The symptoms were severe, and he slept almost all day and night. Seven days before this admission, the patient had an oral temperature of 39.4°C, and headache developed, as well as achiness and stiffness in the arms, shoulders, knees, and legs. He was not able to eat a full meal because of decreased appetite and nausea. He did not have abdominal pain, vomiting, or diarrhea.

Five days before this admission, the fever and headache abated; however, the achiness increased, and the patient noticed that his urine was dark yellow. Three days before this admission, the patient sought evaluation in the urgent care clinic of another hospital. Testing was negative for severe acute respiratory syndrome coronavirus 2, respiratory syncytial virus, and influenza virus types A and B. He was instructed to get adequate rest and hydration. Two days before this admission, the symptoms had not abated, and the patient returned to the urgent care clinic. On examination, new yellow discoloration of the skin and eyes was observed, and he was instructed to go to the emergency department of the other hospital.

On evaluation, the temporal temperature was 36.8°C, the blood pressure 106/70 mm Hg, the pulse 109 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The white-cell count was 17,900 per microliter (reference range, 4500 to 11,000), the platelet count 34,000 per microliter (reference range, 150,000 to 400,000), and the hemoglobin level 15.7 g per deciliter (reference range, 13.0 to 17.0). The creatinine level was 3.0 mg per deciliter (265 μmol per liter; reference range, 0.6 to 1.4 mg per deciliter [53 to 124 μmol per liter]), the total bilirubin level 15.9 mg per deciliter (272 μmol per liter; reference range, 0.0 to 1.2 mg per deciliter [0 to 21 μmol per liter]), and the direct bilirubin level more than 10.0 mg per deciliter

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Table 1. Laboratory Data.*

Variable	Reference Range, Other Hospital	2 Days before Current Admission, Other Hospital	Reference Range, This Hospital†	On Current Admission, This Hospital
Blood				
White-cell count (per μl)	4500–11,000	17,900	4500–11,000	21,700
Differential count (per μl)				
Neutrophils	1500–7800	16,100	1800–7700	15,190
Lymphocytes	1000–4800	500	1000–4800	2410
Monocytes	0–800	1000	200–1200	200
Immature granulocytes	0–90	140	—	—
Hemoglobin (g/dl)	13.0–17.0	15.7	13.5–17.5	10.2
Hematocrit (%)	37.5–50.0	45.2	41.0–53.0	27.6
Platelet count (per μl)	150,000–400,000	34,000	150,000–450,000	67,000
Sodium (mmol/liter)	137–146	129	135–145	124
Potassium (mmol/liter)	3.5–5.3	3.4	3.4–5.0	3.3
Chloride (mmol/liter)	98–107	92	98–108	86
Carbon dioxide (mmol/liter)	23–32	24	23–32	20
Urea nitrogen (mg/dl)	5–25	48	8–25	59
Creatinine (mg/dl)	0.6–1.4	3.0	0.60–1.50	3.36
Glucose (mg/dl)	70–100	117	70–110	81
Magnesium (mg/dl)	—	—	1.7–2.4	1.5
Lactate dehydrogenase (U/liter)	—	—	110–210	298
Haptoglobin (mg/dl)	—	—	30–200	292
Lactic acid (mmol/liter)	0.5–2.0	1.0	0.5–2.0	1.9
Total bilirubin (mg/dl)	0.0–1.2	15.9	0.0–1.0	26.1
Direct bilirubin (mg/dl)	0.0–0.5	>10.0	0.0–0.4	26.1
Aspartate aminotransferase (U/liter)	15–41	50	10–40	44
Alanine aminotransferase (U/liter)	14–63	38	10–55	41
Alkaline phosphatase (U/liter)	40–129	103	45–115	106
Total protein (g/dl)	6.4–8.3	6.2	6.8–8.3	4.9
Albumin (g/dl)	4.0–5.0	3.3	3.3–5.0	2.5
D-Dimer (ng/ml)	0–500	1640	0–500	3486
Fibrinogen (mg/dl)	187–446	>840	150–400	474
Prothrombin time (sec)	—	11.1	11.5–14.5	16.7
International normalized ratio for prothrombin time	—	1.0	0.9–1.1	1.4
Activated partial-thromboplastin time (sec)	—	28.5	22.0–36.6	32.3
Urine				
Bilirubin	Negative	Large	Negative	2+
Urobilinogen	Negative	Trace	Negative	Negative
Blood	Negative	Moderate	Negative	Negative
Glucose	Negative	Positive (250 mg/dl)	Negative	Negative
Ketones	Negative	Trace	Negative	Negative

Table 1. (Continued.)

Variable	Reference Range, Other Hospital	2 Days before Current Admission, Other Hospital	Reference Range, This Hospital†	On Current Admission, This Hospital
Leukocyte esterase	Negative	Trace	Negative	Negative
Nitrites	Negative	Negative	Negative	Negative
Protein	Negative	Positive (300 mg/dl)	Negative	Negative
pH	5.0–8.0	6.5	5.0–9.0	5.5
Specific gravity	1.005–1.030	1.011	1.001–1.035	1.005
Red cells (per high-power field)	0–2	3–5	—	—
White cells (per high-power field)	0–5	6–10	—	—

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

(171 μmol per liter; reference range, 0.0 to 0.5 mg per deciliter [0 to 9 μmol per liter]). Other laboratory test results are shown in Table 1. Blood cultures were obtained. The patient was admitted to the other hospital.

During the subsequent 2 days, the patient received intravenous fluids. On the third hospital day, the blood pressure decreased to 71/60 mm Hg, and the oxygen saturation had also decreased. The creatinine level increased to 3.8 mg per deciliter (336 μmol per liter), the hemoglobin level decreased to 10.3 g per deciliter, and the total bilirubin level increased to 20.9 mg per deciliter (357 μmol per liter). Supplemental oxygen was administered through a nasal cannula, and boluses of intravenous fluids were given. The patient was transferred to this hospital for further treatment.

On evaluation, the patient reported exhaustion and shortness of breath but no cough, rhinorrhea, or congestion. He had no known medical conditions, took no medications, and had no known drug allergies. He lived in an apartment in an urban area of New England with his partner, who had had an acute illness characterized by fever, malaise, nausea, and diarrhea that began 7 days before this admission and resolved after 4 days.

The patient worked in an office, and he took daily walks with his dog through the woods and along a river; he recalled receiving multiple insect bites during these walks. He reported no recent travel. He had smoked one pack of cigarettes per day for 16 years and used marijuana daily. He consumed two alcoholic drinks at a time, a few times per week, and he did not use illicit drugs.

On examination, the temporal temperature was 36.3°C, the blood pressure 100/56 mm Hg, the pulse 103 beats per minute, the respiratory rate 42 breaths per minute, and the oxygen saturation 91% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. He was alert and oriented but appeared ill. He had increased work of breathing, with the use of accessory muscles of respiration; diffuse rales were heard in both lungs. There was no abdominal tenderness, hepatosplenomegaly, asterixis, or leg swelling. Marked scleral icterus and jaundiced skin were present, but he had no conjunctival suffusion, rash, or ulcers. Laboratory test results are shown in Table 1.

Dr. Ryan Chung: Radiography of the chest revealed bilateral, predominantly peripheral, patchy opacities (Fig. 1A). Ultrasonography of the abdomen showed hyperechogenic and prominent portal triads with a "starry sky" appearance; there was no biliary ductal dilatation or hydronephrosis. Computed tomography (CT) of the chest, abdomen, and pelvis, performed without the administration of intravenous contrast material, revealed multifocal consolidative and ground-glass opacities with tree-in-bud nodularity in both

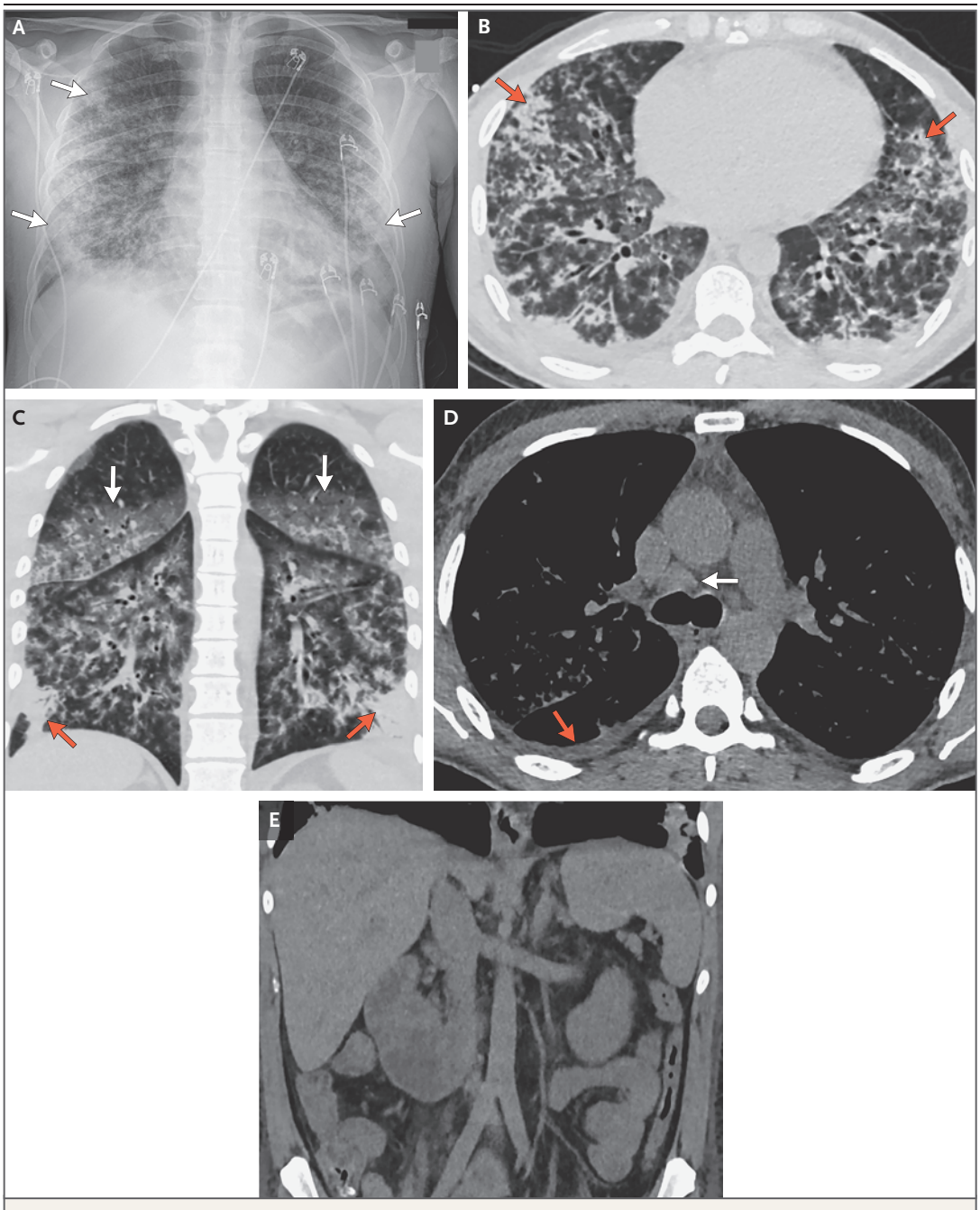

Figure 1. Imaging Studies of the Chest, Abdomen, and Pelvis.

A chest radiograph (Panel A) shows bilateral, predominantly peripheral, patchy airspace opacities (arrows) in both lungs. CT images of the chest, abdomen, and pelvis were obtained without the administration of intravenous contrast material. Axial (Panel B) and coronal (Panel C) CT images of the chest in a lung window show multifocal consolidative opacities (orange arrows) and ground-glass opacities (white arrows) in both lungs. An axial CT image of the chest in a soft-tissue window (Panel D) shows an enlarged mediastinal lymph node (white arrow) and a right pleural effusion (orange arrow). A coronal CT image of the abdomen and pelvis in a soft-tissue window (Panel E) shows no focal liver lesions, biliary ductal dilatation, or hepatosplenomegaly.

lungs (Fig. 1B and 1C), as well as small pleural effusions and enlarged mediastinal and hilar lymph nodes (Fig. 1D). No hepatic lesions, biliary ductal dilatation, or hepatosplenomegaly were noted (Fig. 1E).

Dr. Crabtree: The patient started treatment with continuous positive airway pressure. Empirical treatment with intravenous vancomycin and cefepime and oral doxycycline was administered.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. William C. Hillmann: This previously healthy 37-year-old man presented with an acute, nonspecific febrile syndrome with prominent fatigue, malaise, and myalgia, which was complicated by hypoxic respiratory failure and multiple laboratory abnormalities, including leukocytosis, acute kidney failure, and conjugated hyperbilirubinemia. In constructing a differential diagnosis, I will consider acute febrile illnesses that can occur in a presumed immunocompetent patient and may progress rapidly to critical illness with multisystem organ failure.

ACUTE FEBRILE ILLNESS

Acute febrile illness is a common clinical syndrome with many possible causes. This patient had no obvious localizing symptoms, clinically significant medical history, or prominent epidemiologic risk factors that would help narrow the differential diagnosis. However, the differential diagnosis can be more focused when considering entities that can cause a healthy person to become critically ill extremely quickly.

Cancer and inflammatory conditions can result in acute febrile illness and should be considered. However, this patient's complete blood count does not show any gross abnormalities in the white-cell differential count or blasts that would suggest acute leukemia, and only mild and probably reactive lymphadenopathy was seen on imaging, which would not be consistent with lymphoma. Inflammatory conditions such as antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis can cause severe illness with protean and variable manifestations, including lung, kidney, and skin involvement, and require a high index of suspicion and low threshold for testing. The pulmonary findings on CT in this patient are nonspecific but could be seen in a patient with ANCA-associated vasculitis, even without the classic rash, and testing should be done.

Given the acute onset of this patient's presentation, an infectious cause seems likely. A wide array of bacterial, viral, parasitic, fungal, and tickborne illnesses should be considered. Within each category of potential pathogens, there are typical and atypical pathogens, although what is considered atypical depends on local epidemiologic factors. Infections with viral and parasitic pathogens, such as dengue, chikungunya, and malaria, can manifest with similar clinical signs and symptoms including fever, malaise, and myalgia, all of which were seen in this patient. These diseases are common in tropical areas but rare in New England. Therefore, unless there is a history of travel to a region where these diseases are endemic, they are unlikely causes of this patient's illness.

TICKBORNE ILLNESSES

This patient takes regular walks with his dog and recalls insect bites. Lyme disease, although common in New England, does not typically cause this degree of illness. Anaplasmosis can cause severe illness, anemia, and thrombocytopenia, features that were seen in this patient, but it is more commonly associated with leukopenia and elevated levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Babesiosis is a parasitic infection with manifestations similar to those of malaria, including severe illness with thrombocytopenia, acute kidney failure, and respiratory failure, features that were observed in this case. However, because babesiosis is associated with hemolytic anemia, the presence of unconjugated hyperbilirubinemia would be expected. Tickborne rickettsial diseases, such as Rocky Mountain spotted fever, can cause severe illness with thrombocytopenia and abnormalities in the results of liver function tests. Rocky Mountain spotted fever has historically been rare in New England, but the incidence may be increasing in this area, possibly because of climate change and associated seasonal warming. This patient does not have the typical rash; however, the rash may appear

later in the disease course, after severe illness occurs, or it may not develop at all, as in cases termed "spotless" fever. Therefore, rickettsiosis is difficult to rule out.

FUNGAL INFECTIONS

This patient has no known risk factors (e.g., intravenous substance use or immunosuppression) for invasive fungal disease caused by typical fungal pathogens such as candida. Endemic fungal infections, such as coccidioidomycosis, blastomycosis, and histoplasmosis, can be considered. Coccidioidomycosis is unlikely in this patient because he has no history of travel to the southwestern United States. Blastomycosis can cause extrapulmonary disease but most commonly leads to skin lesions, osteomyelitis, and central nervous system disease. Although blastomycosis can cause severe disease, this patient has no history of travel to the Midwest or southeastern United States. Histoplasmosis is associated with severe illness and respiratory failure; however, pneumonia associated with histoplasmosis tends to be an early finding because transmission occurs through inhalation of spores. None of these endemic mycoses typically cause the pattern of liver injury that was seen in this patient.

VIRAL INFECTIONS

Epstein–Barr virus and cytomegalovirus can both result in disease with multiorgan involvement, but they rarely cause severe disease in the absence of immunosuppression. Hepatic involvement with Epstein–Barr virus or cytomegalovirus is typically characterized by hepatitis, not isolated hyperbilirubinemia. Infection with acute human immunodeficiency virus (HIV) can manifest with a nonspecific acute febrile illness, but hyperbilirubinemia would be an unusual finding in a patient with an acute retroviral syndrome. A thorough review of risk factors should be performed in this patient, and testing should be done if any are identified.

CONJUGATED HYPERBILIRUBINEMIA

When a thorough diagnostic evaluation guided by structured consideration of clinical symptoms, immunocompetence, epidemiologic factors, and laboratory values has not yet yielded an answer, it can be helpful to consider a unique laboratory or clinical feature to broaden the differential diagnosis. Many of the clinical findings in this patient are nonspecific. Fever, myalgia, leukocytosis, acute kidney failure, respiratory failure, and imaging abnormalities are common findings in patients with any type of severe infection; however, the severe and isolated conjugated hyperbilirubinemia is an unusual finding.

The differential diagnosis for conjugated hyperbilirubinemia without cholestatic injury in an adult is not extensive. The Rotor syndrome and the Dubin–Johnson syndrome, which result from congenital errors of bilirubin metabolism, can include mild conjugated hyperbilirubinemia, but they would not account for the other features of this patient's illness. Infectious causes of conjugated hyperbilirubinemia — including cholangitis, hepatic abscess, and tuberculosis, among others — are typically associated with cholestasis, and cholestatic injury was not present in this patient. However, one infectious cause that is particularly associated with this laboratory abnormality and the other features of this patient's presentation is leptospirosis.

LEPTOSPIROSIS

Leptospirosis is a zoonotic spirochetal infection that is most prevalent in tropical environments. Humans can acquire leptospirosis through contact with urine from infected mammals (often rats) or through exposure to a freshwater environment contaminated with the urine. Although leptospirosis is relatively uncommon in New England, this patient regularly walked his dog by a river, and it is possible that swimming in the river or having water splash onto a mucous membrane could account for his exposure. We do not know whether his dog had received the leptospirosis vaccine, which is commonly administered to dogs in this region.

Leptospirosis most often manifests as a mild, self-limited, nonspecific febrile illness; however, in 10 to 15% of cases, it can progress to icteric leptospirosis, also known as Weil's disease. Icteric leptospirosis is characterized by fever, progressive multisystem organ failure, acute kidney failure, and conjugated hyperbilirubinemia (the mechanism for conjugated hyperbilirubinemia is not known).[1,2] Other complications can include conjunctival suffusions, pulmonary hemorrhage, and myocarditis. The respiratory failure and

hypotension observed in this case could have resulted from pulmonary hemorrhage or myocarditis (or both).

Although this patient does not have the characteristic risk factor of travel to a tropical region, he has a dog and possible freshwater exposure, and the clinical syndrome and unique laboratory abnormalities are consistent with a diagnosis of leptospirosis, specifically icteric leptospirosis. I would recommend obtaining a liver-biopsy specimen to stain for leptospira species, as well as serologic testing and nucleic acid amplification testing (NAAT) to establish the diagnosis of leptospirosis.

DR. WILLIAM C. HILLMANN'S DIAGNOSIS

Leptospirosis.

PATHOLOGICAL DISCUSSION

Dr. Miranda E. Machacek: Testing for ANCAs was negative, and the patient underwent a percutaneous, nonfocal liver biopsy with ultrasonographic guidance. Histologic examination of the biopsy specimen showed a smooth liver contour and normal lobular architecture (Fig. 2A). Portal tracts contained a mixed inflammatory infiltrate that was composed of neutrophils and mononuclear cells, such as lymphocytes. Neutrophils were also seen circulating in the adjacent sinusoids, and many left-shifted band forms were present. One portal tract contained bile ducts with prominent eosinophilic cytoplasm, which is a reactive, nonspecific change (Fig. 2B). The lobules showed scattered hepatocyte mitotic activity (Fig. 2C). In addition to neutrophils, nucleated red cells were present in the sinusoids (Fig. 2D), as were rare megakaryocytes. Steiner staining, periodic acid–Schiff staining with diastase, and immunohistochemical staining for spirochetes were performed at this hospital and did not reveal any microorganisms. The mixed inflammation in the portal tracts with a leukoerythroblastic reaction and regenerative hepatic parenchyma were mild, nonspecific findings that were suggestive of a reactive process. Possible causes included infection or drug-induced liver injury, and additional microbiologic and serologic testing was recommended.

LABORATORY TESTING

Dr. Robyn A. Stoddard: Leptospira species are spiral-shaped, long (6 to 20 μm), and thin (0.1 μm) gram-negative bacteria.[3,4] The diagnosis of leptospirosis can be made through direct detection of the organism, which can be done with various methods, or through detection of leptospiral antibodies (Fig. 3).[3,5,6]

The type of specimen to obtain and the appropriate test to perform for the diagnosis of leptospirosis depend on the time since the onset of symptoms.[3,5,6] In the first week of symptoms, it is recommended that whole blood be obtained for NAAT.[5,6] In addition, serum should be obtained for serologic testing; antibodies, specifically IgM antibodies, can be found in the blood 5 to 7 days after the onset of symptoms.[3,5] IgM antibodies can persist for months to years after exposure and can cross-react with other organisms, so caution should be taken when interpreting results.[3,5,6] Assays that detect IgM antibodies are more diagnostically sensitive than microscopic agglutination testing (MAT) in the acute phase of leptospirosis.[6,7] Serum is less sensitive than whole blood for nucleic acid testing, but it can be used if whole blood is not available.[8] After the first week of symptoms, urine is the preferred specimen for NAAT.[5,6] If the patient has neurologic symptoms, cerebrospinal fluid should be obtained for polymerase-chain-reaction testing. In addition, a serum sample obtained during the convalescent phase of illness (convalescent serum sample) should be used for screening assays, which can also be paired with a serum sample obtained during the acute phase (acute serum sample), if available, for MAT.[3]

Serologic assays for detecting IgM or IgG antibodies to leptospires can be divided into screening and confirmatory tests.[9] Rapid-detection tests are simple screening tests that require no specialized equipment,[5] whereas other screening tests require equipment and technical expertise. Serum was obtained from this patient 11 days after the onset of symptoms and was sent to a reference laboratory for serologic testing by means of an IgM enzyme-linked immunosorbent assay, which was positive for IgM antibodies to leptospires. The only confirmatory serologic assay for leptospirosis is MAT, which detects both IgM and IgG antibodies, but it has low sensitivity

in the acute phase and was not performed in this case.[3,5,6]

The isolation of leptospires or the detection of leptospira DNA in a clinical sample is another confirmatory approach for leptospirosis.[9] Culture of leptospires is difficult and time-intensive. Leptospires require specific media that must be inoculated shortly after the clinical sample, such

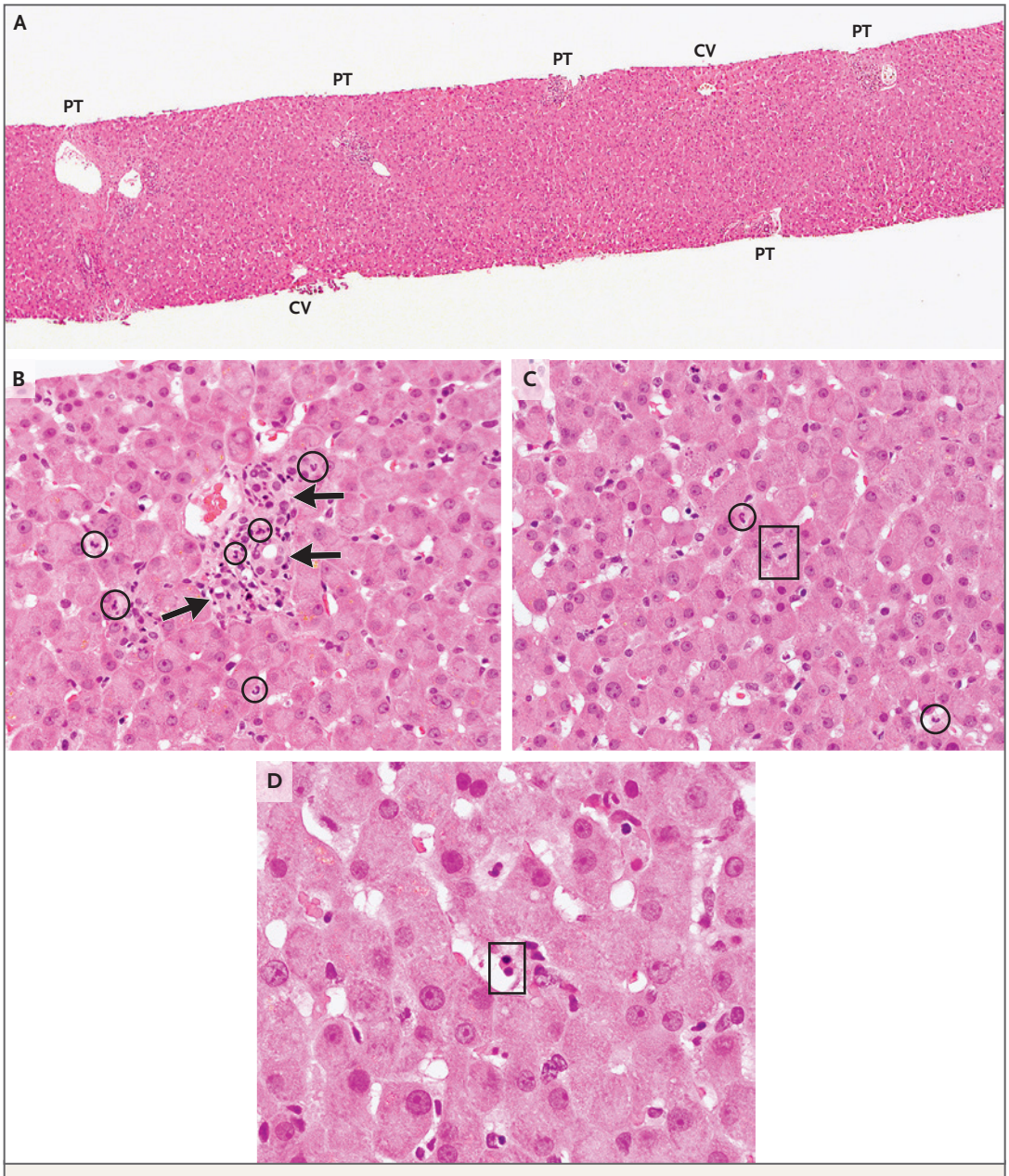

Figure 2. Biopsy Specimen of the Liver.

A percutaneous, nonfocal liver biopsy was performed. Hematoxylin and eosin staining of the biopsy specimen (Panel A) shows a smooth contour and normal lobular architecture, including portal tracts (PT) and central veins (CV). Higher magnification of a portal tract (Panel B) shows mixed inflammation, including neutrophils (circles) and mononuclear cells, along with nonspecific, reactive changes in the bile ducts (arrows). Higher magnification of lobules (Panels C and D) shows circulating neutrophils with left-shifted band forms (circles), scattered mitotic figures (Panel C, rectangle), and nucleated red cells (Panel D, rectangle).

as whole blood or urine, is obtained; they have difficulty surviving in urine.[3,5,6] It can take 6 weeks or longer for growth to be detected. For this reason, cultures are prone to contamination by other organisms.[5,6] The processing time of molecular assays, specifically NAAT, is substantially shorter than that of culture. Whole-blood and urine specimens from this patient, obtained 11 days after the onset of symptoms, were sent to the Centers for Disease Control and Prevention (CDC). NAAT was positive in the whole-blood specimen but was negative in the urine specimen. The NAAT performed for this patient targeted *lipL32* (the gene encoding the 32-kDa lipoprotein), which is found only in pathogenic leptospires.[10,11] There is a narrow window of bacteremia, and leptospires are intermittently shed in urine, which limits the effectiveness of nucleic acid testing.[3,5,6]

It is notable that NAAT had different results in blood and urine in this case. This difference might be explained by the intermittent shedding of leptospires in urine or the possibility that the bacteria had not infected the renal tubules, although testing had been performed more than a week after the reported onset of symptoms. It is recommended that multiple types of tests with multiple specimen types be performed at several time points if the initial tests are negative (Fig. 3).[6] It is important to note that treatment with antimicrobial drugs could limit the detection of organisms and decrease the antibody response.[6] Treatment should not be delayed while waiting to obtain clinical samples to test for leptospirosis.

LABORATORY DIAGNOSIS

Leptospirosis.

DISCUSSION OF MANAGEMENT

Dr. Amir M. Mohareb: Leptospirosis is one of the most widespread zoonotic infections in the world. The bacteria can infect the renal tubules and are shed in the urine of infected mammals. Many mammals act as reservoirs of the bacteria, with rodents being the most common carriers in urban

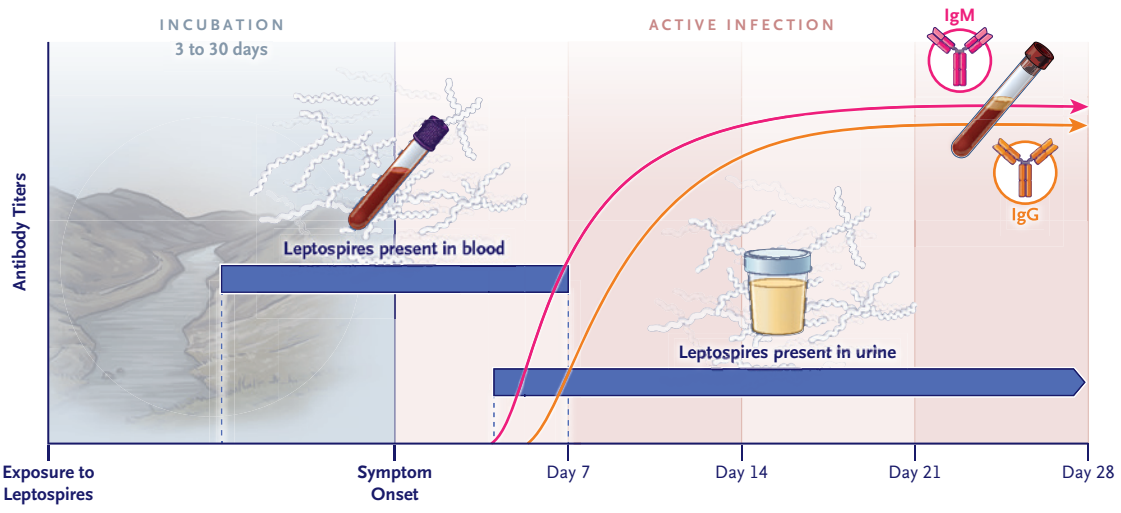

Figure 3. Phases of Leptospirosis and Diagnostic Testing.

The diagnosis of leptospirosis can be made through direct detection of the organism, which can be done with various methods, or through detection of antibodies to leptospires. In the first week after the onset of symptoms, leptospires are present in the blood, and nucleic acid amplification testing (NAAT) of whole blood is recommended. If whole blood is not available, then serum can be used, but it is less sensitive. During the first week after the onset of symptoms, IgM and IgG antibodies can be found in the blood. An acute serum sample should be obtained for IgM testing and microscopic agglutination testing (MAT). Beyond the first week after the onset of symptoms, leptospires may be present in the urine, at which point urine is the preferred specimen for NAAT. However, shedding of leptospires in the urine is intermittent, which limits the effectiveness of NAAT, so testing at multiple time points may be helpful. Convalescent serum samples should also be obtained for IgG testing and MAT. After 4 weeks, IgM and IgG antibodies may persist.

areas. Humans can become infected when they come into contact with contaminated water, soil, or other parts of the environment. Risk factors for leptospirosis include habitation in crowded, impoverished urban settings with rodent infestation; occupational exposures in agriculture, veterinary medicine, and sewers and water treatment; and exposures to pet dogs and domesticated livestock, particularly around freshwater sources. Contact with stagnant water and freshwater swimming are additional risk factors. This patient probably acquired leptospirosis from close contact with his pet dog, with contaminated freshwater as the source of the bacteria. Later in the hospitalization, the patient recounted that in addition to regular walks with his dog, he recalled an episode in which the dog had jumped into the river. The timing of this episode would have been consistent with the time course of this patient's illness. The incubation period of leptospirosis is 3 to 30 days; however, symptoms develop in most people, as in this patient, within 2 weeks after exposure.

The global burden of leptospirosis may be increasing, possibly owing to the combination of climate change and urbanization.[12,13] More than 1 million cases of leptospirosis are estimated to occur around the world each year. Extreme weather events that involve flooding may precipitate outbreaks by facilitating transmission from environmental and animal reservoirs to humans. Numerous outbreaks of leptospirosis have been reported after flooding events.[12] Urbanization can contribute to outbreaks through urban overcrowding, which facilitates stormwater flooding and increases the likelihood of human contact with rodent vectors.

Leptospirosis has a variety of clinical manifestations (Fig. 4), and making the diagnosis in

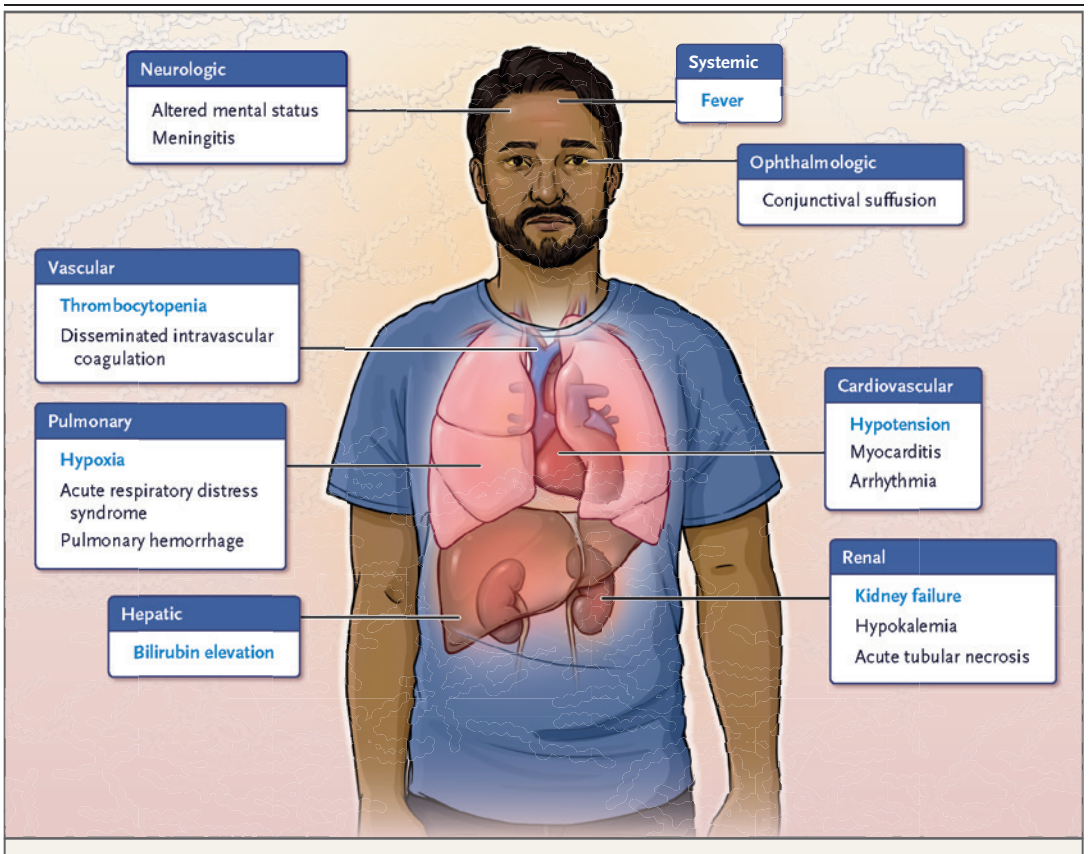

Figure 4. Clinical Manifestations of Leptospirosis.

Leptospirosis can manifest with a wide array of possible clinical signs and symptoms. The features present in this patient (shown in blue) include fever, thrombocytopenia, hypoxia, hypotension, kidney failure, and a markedly elevated bilirubin level.

resource-limited settings is a challenge, particularly because other infections can manifest with overlapping syndromes. Outbreaks of dengue virus infection often co-occur with leptospirosis, and the common clinical presentations of the two diseases make them very hard to distinguish.[14] Malaria, yellow fever, influenza, and hantavirus infection are among the other infections that have overlapping syndromes with leptospirosis.[15] Patients with rickettsial diseases can also present with similar signs and symptoms, such as fever, malaise, thrombocytopenia, and liver injury. It usually takes several days to receive test results for leptospirosis, so if the diagnosis is suspected, we do not wait for a positive test before starting empirical therapy.

Despite the wide array of clinical signs and symptoms, most cases of leptospirosis are self-limited. Patients who have icteric leptospirosis may have fever, hyperbilirubinemia, and acute kidney failure (as in this case). Patients may also have conjunctival suffusion on examination. Pulmonary hemorrhage, which portends a poor prognosis, develops in a small fraction of patients. In this patient, the diffuse airspace opacities and respiratory failure that developed concurrently with a decrease in the hematocrit could have been indicative of pulmonary hemorrhage. The hypotension in this patient could have been related to either circulatory or cardiovascular compromise with possible myocarditis, which can occur in patients with severe disease. Aseptic meningitis, uveitis, and other nervous system manifestations may also occur in patients with icteric leptospirosis.

The mainstay of management for icteric leptospirosis is supportive care for end-organ damage. Such care includes oxygen supplementation and ventilatory support for patients with acute respiratory distress syndrome, as well as renal replacement therapy for patients with anuric acute kidney failure. Mild leptospirosis can be treated with doxycycline, azithromycin, or amoxicillin. Severe disease, such as that seen in this patient, should be treated with intravenous ceftriaxone or doxycycline. Adjunctive therapies, such as glucocorticoids and plasmapheresis, have been used in some cases of severe icteric disease; however, high-quality evidence supporting their use is limited. In most cases, patients recover without the use of antimicrobial therapy. When this patient presented to the hospital, the probability of leptospirosis was high enough that we initiated empirical doxycycline therapy while awaiting the results of diagnostic testing.

FOLLOW-UP

Dr. Crabtree: Treatment with doxycycline was continued while the results of tests for leptospirosis were pending. The use of empirical vancomycin and cefepime therapy was discontinued once cultures of the blood had been negative for 48 hours. On the fifth hospital day, the white-cell count peaked at 54,950 per microliter, and the direct bilirubin level peaked at 39.0 mg per deciliter (667 μmol per liter); the creatinine level had improved and was 1.59 mg per deciliter (141 μmol per liter). The hypoxia, which could have been related to pulmonary hemorrhage, resolved; the acute kidney failure, which was attributed to acute tubular necrosis, abated. On the eighth hospital day, the white-cell count decreased to 18,870 per microliter, the direct bilirubin level to 26.1 mg per deciliter (369 μmol per liter), and the creatinine level to 1.4 mg per deciliter (124 μmol per liter). The patient was discharged home.

At home, the patient completed a 14-day course of doxycycline. The color of the skin, urine, and stool gradually returned to normal, and the malaise and fatigue were slow to abate. One month after discharge, the acute kidney failure had resolved; 2 months after discharge, the hyperbilirubinemia had resolved. Now, 11 months after discharge, the patient still struggles to cope with the mental health effects of the medical trauma related to his critical illness and hospitalization.

FINAL DIAGNOSIS

Icteric leptospirosis.

The findings and conclusions are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

This case was presented at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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