A 46-year-old Hispanic woman presented to a Minnesota emergency department in late fall 2020 with 5 days of fever (38.3°C), chills, malaise, headache without photophobia, epistaxis with loss of smell, gingival bleeding when brushing her teeth, nonproductive cough, diarrhea, and diffuse myalgia when driving home from a trip just across the Texas-Mexico border. She never had similar symptoms before, but has traveled to Mexico on multiple occasions. Her exposures in Mexico included domesticated dogs, mosquito bites, local food, and sexual intercourse while in a monogamous relationship. She denied outdoor camping or exposure to stagnant water. Another relative in Mexico developed similar symptoms. Her medical comorbidities included uncontrolled type 2 diabetes mellitus with the last hemoglobin A1c value of 13.2% (4.2 to 5.6%), hypertension, morbid obesity, hyperlipidemia, mild intermittent asthma, and previous cholecystectomy.

Physical examination revealed a Hispanic woman in no acute respiratory distress but appeared uncomfortable. She was afebrile with heart rate 88 beats/min and blood pressure 113/74 mm Hg and saturating appropriately on room air. No conjunctivitis, nuchal rigidity, abdominal tenderness to palpation, or cardiopulmonary abnormalities were notable, but scattered petechiae were present over bilateral lower extremities. Laboratory values were notable for the following (reference ranges shown parenthetically): hematocrit, 43.0% (35.5 to 44.9%); white blood cell count, 3.3×10⁹/L (3.4 to 9.6×10⁹/L); platelet count, 20×10⁹/L (157 to 371×10⁹/L); bicarbonate level, 19 mmol/L (22 to 29 mmol/L); creatinine level, 0.57 mg/dL (0.59 to 1.04 mg/dL); total bilirubin level, 0.9 mg/dL (<1.2 mg/dL); alanine aminotransferase level, 196 U/L (7 to 45 U/L); aspartate aminotransferase level, 378 U/L (8 to 43 U/L); alkaline phosphatase level, 715 U/L (35 to 104 U/L); albumin level, 3.0 g/dL (3.5 to 5.0 g/dL); D-dimer level, 3122 ng/mL (<500 ng/mL); international normalized ratio, 1.1 (0.9 to 1.1); activated partial thromboplastin time, 44 seconds (25 to 37 sec); and fibrinogen level, 233 mg/dL (200 to 393 mg/dL). The lactate level was within normal limits. The result of urine pregnancy testing was negative. Peripheral smear revealed atypical reactive lymphocytes without schistocytes or morulae. Blood cultures were obtained. Computed tomography (CT) of the chest, abdomen, and pelvis was notable for periportal edema and trace ascites. There was no evidence of pulmonary embolism or CT findings suggestive of coronavirus disease 2019 (COVID-19). The result of rapid COVID-19 testing was undetectable.

Because of patient-specific exposures, a broad differential diagnosis was entertained including various viral and bacterial etiologies.

1. Which one of the following tests would be the most appropriate to evaluate for possible bacterial causes of this patient’s presentation?
   a. Leptospira antibodies
   b. Rickettsial antibodies
   c. Anaplasma antibodies
   d. Stool culture
   e. Borrelia antibodies

Leptospirosis has a similar incubation period and can manifest with fever, myalgia, and headache. Patients with leptospirosis have similar hematologic and liver function test abnormalities as well. However, this infection is less likely given the lack of exposure to contaminated water, lack of...
conjunctival suffusion, normal renal function, and a relative with similar symptoms in an urban environment. Rocky Mountain spotted fever also presents with similar symptoms and thrombocytopenia and can be acquired in Texas and Northern Mexico. However, infection outside of late spring or summer, as well as lack of a centripetal blanching maculopapular rash, makes this disease less likely. Anaplasmosis, although highly prevalent in Minnesota and often complicated by thrombocytopenia, leukopenia, and elevated liver function tests, is unlikely to be acquired in fall along the Texas-Mexico border. Further, hemorrhagic sequelae are rare in anaplasmosis in the United States, but case series have been reported in China. Typhoid fever due to salmonella infection should be suspected in a patient with multiple days of fever, diarrhea, leukopenia, and elevated aminotransferase levels returning from an endemic area such as Mexico, and a stool culture should be obtained. Disseminated Lyme disease is unlikely to be acquired in late fall in Mexico and is not associated with severe thrombocytopenia.

A stool culture was ordered. Human immunodeficiency virus (HIV) and hepatitis A, B, and C virus test results were negative. Although the cytomegalovirus IgG antibody result was positive, the IgM antibody result was negative, as well as a Monospot test. A tourniquet test was performed at bedside. The blood pressure cuff was inflated halfway between the systolic and diastolic pressure readings for 5 minutes and then removed.

2. Which one of the following is suggestive of a positive tourniquet test result?
   a. Ten or more petechiae develop just proximal to the blood pressure cuff
   b. Ten or more petechiae develop under the area of the blood pressure cuff
   c. Ten or more petechiae develop in a 2.5 cm square in the antecubital fossa
   d. Ten or more petechiae develop across the entire arm
   e. Presence of any petechiae during the cuff inflation distal to the antecubital fossa.

   A positive tourniquet test result is suggestive of increased vascular permeability and is frequently used in resource-limited settings to distinguish dengue from other viral illnesses and stratify severity of disease, despite the variable reported sensitivity and specificity of the bedside test. The test is performed by inflating the blood pressure cuff between the systolic and diastolic pressure values, so that venous return is occluded but arterial flow remains unimpeded. This preferentially increases venous pressure just distal to the blood pressure cuff, not proximally or underneath the cuff. To standardize the examination, a positive tourniquet test result is defined as 10, but in older literature 20, or more petechiae that develop in a 2.5 cm square in the antecubital fossa. Petechiae may develop distally across the arm, but are more likely to develop closer to the antecubital fossa.

   The result of the tourniquet test was positive.

3. Which one of the following clinical features is more suggestive of dengue infection rather than infection with Zika or chikungunya?
   a. Conjunctivitis
   b. Headache
   c. Rash
   d. Myalgia
   e. Gingival bleeding

   Differentiating between dengue, Zika, and chikungunya is difficult because of the overlap in both clinical syndromes and endemic regions, including the area in Northern Mexico where this patient traveled. Furthermore, coinfection with multiple viruses is not uncommon. Conjunctivitis was not present in this patient and is more characteristically present in Zika or chikungunya infections, not dengue. Headache, rash, and myalgia are symptoms shared by all 3 diseases and are not helpful in distinguishing between them. Gingival bleeding, which was present in this patient, and other hemorrhagic sequelae are more unique to dengue and help differentiate this disease...
entity from Zika and chikungunya, but this occurs in only severe dengue infections.1,5

The patient’s diarrhea had resolved shortly after admission on day 5 of her illness. The stool culture result was negative.

4. Which one of the following tests at this time would best help differentiate between primary and secondary dengue infections?
   a. Nonstructural protein 1 (NS1) antigen
   b. Reverse transcription polymerase chain reaction (RT-PCR) testing for dengue
   c. Dengue IgM antibody
   d. Dengue IgG antibody
   e. Viral isolation by mosquito inoculation

Choosing the appropriate test to confirm dengue infection depends on the number of days the patient is symptomatic. Similarly, differentiating the first infection (primary) from the subsequent infections (secondary) is also influenced by the timing of the disease course. Nonstructural protein 1 antigen is produced by the dengue virus and can be detected up to 7 to 9 days after symptom onset. Although the sensitivity of the test may be slightly lower in secondary infections because of the host antibody response, this test result may be positive in both primary and secondary infections. Similarly, RT-PCR test results will remain positive within 5 days of both primary and secondary disease. Dengue IgM antibodies can be present as early as day 4 of illness. Although dengue IgM antibody titers are often higher in primary infection than in secondary infection, the single test without paired sera may not differentiate. Dengue IgG antibodies, which are not expected to rise until 6 to 15 days of illness, should result positive at this time in a secondary dengue infection but not primary infection.1,6-8 Viral isolation can be accomplished by mosquito or mammalian cell inoculation and is rarely used for serotype identification, but this would not be helpful in a patient without previous microbiological data.7

The dengue IgG antibody, RT-PCR testing for dengue, and the NS1 antigen test results were all positive, whereas the dengue IgM antibody result was equivocal, suggestive of active secondary infection. Results of RT-PCR and serology testing for Zika and chikungunya were negative. The patient’s family member, who resides in Mexico, was also diagnosed with dengue. On repeat evaluation, vital signs were notable for heart rate 99 beats/min, compared with 88 beats/min on admission; blood pressure 92/69 mm Hg, compared with 113/74 mm Hg on admission; and respiratory rate 20 breaths/min, without fever. A repeat hematocrit was 43.1% (35.5 to 44.9%), compared with 43.0% (35.5 to 44.9%) on admission; and the platelet count was 17×10^9/L (157 to 371×10^9/L), compared with 20×10^9/L (157 to 371×10^9/L) on admission. Additional petechiae were present on the lower extremities.

5. Changes in which one of the following parameters are the most concerning for clinical decompensation?
   a. Platelet count
   b. Hematocrit
   c. Pulse pressure
   d. Respiratory rate
   e. Petechiae

Vigilance for signs and symptoms of progression of dengue infection to severe or shock syndrome is imperative in the supportive management of this disease, especially in patients who may have had previous dengue exposure/infection such as individuals traveling from an endemic area. The platelet count dropping below 20×10^9/L (157 to 371×10^9/L) is often observed in the critical phase of dengue, but only may imply impending shock.6 Although an increase in hematocrit of 20% from baseline hematocrit is suggestive of worsening hemocoagulation and severe plasma leakage, this can be influenced by fluid resuscitation and does not classify shock.1 In this patient, the pulse pressure decrease from 39 mm Hg on admission to 23 mm Hg is an early sign of impending dengue shock syndrome, with the criterion threshold being 20 mm Hg or lower.1,6,8,9 Although the respiratory rate can be
elevated simply because of the underlying infectious process, it may also result from pleural fluid accumulation from plasma leakage, suggestive of severe disease, but not shock. Petechiae can be present in the early febrile stage of dengue and are not suggestive of impending shock.1,6,8,9

The patient was encouraged to increase oral intake and received supplemental parenteral intravenous fluids totaling near 4 liters that day, with return to normotension the following day. Within 3 days, the patient’s thrombocytopenia and liver function tests had improved and she was dismissed from the hospital.

DISCUSSION

Dengue is a single-stranded RNA virus that is transmitted by the Aedes mosquito, with 4 serotypes prevalent in tropical and subtropical climates around the world. Dengue incidence worldwide is increasing, with an estimated 390 million infections per year, of which approximately 96 million become symptomatic.6,8,10 Most dengue cases diagnosed in the United States are travel related, but dengue can be acquired in Texas, Hawaii, or Florida.1,6,8 The clinical presentation of primary dengue is variable, with many infections being asymptomatic. Patients with secondary infections often present with acute fever, headache, myalgia, and rash, with spontaneous resolution of illness in 7 to 9 days. Aside from petechiae that were present in this patient, cutaneous manifestations of dengue infection include diffuse erythematous macules, occasionally scarlatiniform but often coalescing, sparing palms and soles, with small areas without involvement termed “islands of white.”1,6 Diarrhea, which was transient in this patient, is not a common symptom of dengue infection.1 Laboratory abnormalities include leukopenia, thrombocytopenia, transaminitis, and rarely renal dysfunction.1,6

The differential diagnosis for patients who present with early symptoms of dengue is broad and should be guided by patient-specific environmental exposures and symptoms. One should consider etiologies including malaria, typhoid, leptospirosis, anaplasmosis, borreliosis, relapsing fever, and Rocky Mountain spotted fever. There is a considerable overlap in geographical distributions of malaria and dengue, and if testing for one disease, the other should be tested for as well. Viral infection with HIV, COVID-19, Zika, chikungunya, viral hepatitis, Ebstein Barr-Virus, cytomegalovirus, and other hemorrhagic fevers such as yellow fever should also be considered.1 Despite a reportedly monogamous relationship and no suggestive findings on CT of the chest, HIV by RNA and COVID-19 by RT-PCR testing should be ruled out because of the variable multisystem involvement of these viral infections. Yellow fever is endemic to 48 countries in South America and Africa, but not found in Mexico.1 Therefore, it was not considered in this patient. Selecting appropriate testing to confirm the clinically suspected diagnosis of dengue is dependent on the number of days after the start of illness. In early disease, NS1 antigen testing and RT-PCR testing for dengue are most likely to confirm active viremia. After day 4 of illness, a positive dengue IgM antibody result is confirmatory for active disease in patients with no previous exposure or a history of infection. Rapid increase in IgM antibody titers is also suggestive of active infection. The dengue IgG antibody result becomes positive 6 to 15 days after primary infection and, if present early in confirmed disease, is suggestive of secondary infection.1,6,8 Coinfection with Zika or chikungunya can occur and should be tested even if clinical suspicion for dengue is high,4 as Zika infection has implications for men and women of childbearing age. Vaccination against other flaviviruses including yellow fever, tick-borne encephalitis, or Japanese encephalitis may cause false-positive dengue serologies.11

 Appropriately identifying and triaging patients with early dengue is important, as patients with secondary infections may progress to the critical phase of illness 3 to 7 days after illness onset. Mortality in the critical phase may be as high as 20% without treatment, either from hemorrhagic sequelae or systemic plasma leakage causing hypoxemic...
respiratory failure from pleural effusions or death from systemic circulatory failure.\textsuperscript{1,6,8} The major risk factor for severe disease is secondary infection, particularly with a different serotype than before, as severe disease with primary infection is rare.\textsuperscript{1,2} Secondary infection should be suspected primarily in people who live in or travel frequently to endemic areas, which was the case with this patient. Additional risk factors include extremities of age and comorbid conditions such as asthma and diabetes.\textsuperscript{1,2} The World Health Organization (WHO) recommends that patients seen in the outpatient setting should be considered for hospital admission if they exhibit any warning signs such as abdominal pain, recurrent vomiting, extravascular volume accumulation such as ascites or pleural effusion, bleeding, hepatomegaly, orthostasis or dehydration, increasing hematocrit, or other end organ damage. Additional factors that should affect the decision for hospitalization include severity of comorbidities and level of social support.\textsuperscript{1,2}

In 1997, the WHO classified 3 stages of disease: dengue fever, dengue hemorrhagic fever, and dengue shock syndrome (DSS). The diagnosis of dengue fever was satisfied when a patient presenting with the suggestive syndrome had laboratory confirmation of dengue infection. Dengue hemorrhagic fever requires a platelet count below 100×10\textsuperscript{9}/L (157 to 371×10\textsuperscript{9}/L), evidence of plasma leakage such as a hematocrit increase of 20\% from baseline, pleural effusions or ascites, and bleeding diathesis such as a positive tourniquet test result or spontaneous bleeding. Lastly, DSS was classified as the development of hypotension or pulse pressure below 20 mm Hg.\textsuperscript{1,9} In our case, the patient met the 1997 WHO criteria for dengue hemorrhagic fever and may have met criteria for DSS if it were not for timely recognition of clinical decompensation and supplemental fluid administration. In 2009, the WHO updated the classification scheme: dengue without warning signs, dengue with warning signs, and severe dengue.\textsuperscript{1,2} Although these criteria have not been universally adopted, they emphasize recognition of the warning signs that should prompt consideration of hospitalization, as discussed above. Patients meet criteria for severe dengue if they develop shock, respiratory failure from fluid accumulation, severe bleeding, altered mentation, liver transaminase test values greater than 1000 IU/L (7 to 45 U/L), or other organ failure.\textsuperscript{1,2}

During all stages of illness, treatment of dengue is supportive and may include intravenous fluids, correction of metabolic abnormalities, treatment of complications from plasma leakage, and blood transfusions.\textsuperscript{1,6,8,12} With appropriate medical care, prognosis is favorable with 99\% survival rate.\textsuperscript{8} Hospital discharge criteria include general clinical improvement, lack of fever for 48 hours, improvement in platelet count, and stable hematocrit without the need for intravenous fluids.\textsuperscript{1,2} After acute infection, most patients are asymptomatic, but up to 57\% of patients may experience fatigue or arthralgias in the years after infection.\textsuperscript{6,8} In this case, the patient visited her primary care physician a week later, reporting overall improvement but with persistent, though mild, fatigue.

Lastly, dengue is a preventable disease. Personal prevention techniques include reducing time around stagnant water or known breeding sites, using screens and air conditioning, reducing exposed skin with appropriate clothing, and applying insect repellants, particularly during the daytime when \textit{Aedes aegypti} mosquito bites are more common.\textsuperscript{1,12} Although not available in the continental United States, CYD-TDV (Chimeric yellow fever–dengue virus tetravalent dengue vaccine) is a live attenuated vaccine approved for patients living in endemic regions with a laboratory-confirmed dengue infection history.\textsuperscript{11} Patients who received the live attenuated vaccine without primary infection developed severe dengue at a higher rate and should not receive it.\textsuperscript{11} Travelers to endemic regions, including this patient, should be counseled regarding these precautions to reduce the risk of recurrent dengue infection.
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REFERENCES

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