CLINICAL VIGNETTE

An Unwanted Souvenir: Dengue in a Returning Traveler

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Case presentation

A 44-year-old woman was presented with two weeks of intermittent fevers. She reported intermittent evening fevers as high as 101-102 degrees F. Her fevers were associated with a persistent retro-orbital headache, malaise, night sweats, and anorexia. Fevers and headache were responsive to high dose ibuprofen, however both would return the following day. She denied cough, sore throat, rhinorrhea, rash, arthralgias, diarrhea, nausea or vomiting, dysuria, hematuria, or glandular swelling. The only new medication was the resumption of an oral contraceptive one month prior to symptom onset. She had traveled to the Cayman Islands six weeks prior to symptom onset and recalled several mosquito bites while there. She also reported having unprotected sex during travel. She was screened for sexually transmitted diseases after exposure, and she tested negative for HIV, hepatitis B and C, and gonorrhea and chlamydia. She was found to have a yeast infection and bacterial vaginosis, for which she completed fluconazole and metronidazole vaginal gel therapy, respectively, prior to the onset of fevers.

Her past medical history is significant for hypothyroidism for which she takes levothyroxine 175mcg daily. She has allergies to penicillin and sulfa antibiotics. She has no significant family history. She is a non-smoker, drinks alcohol occasionally, and denies drug use. Her active medications include levothyroxine 175mcg daily, cholecalciferol 2000IU daily, and norethindrone acetate-ethinyl estradiol/ferrous fumarate 1-20 mg-mcg.

On evaluation, her blood pressure was 130/70 mm Hg, pulse 106, temperature 36.9 °C, respirations 20, saturation 97% on room air. She was well appearing. HEENT exam was normal. Lymphatic system was positive for fullness in the cervical chain without tenderness. The neck was supple. Her cardiovascular and lung exam were normal. Her abdomen was non-distended without hepatosplenomegaly. She had no edema.

Her neurologic exam was normal. She had no rashes or synovitis. Her laboratory tests were significant for a normal blood count, CO2 level 19, creatinine 1.16, AST 176, ALT 199, and trace blood in the urine. RPR, HIV, hepatitis A IgM, hepatitis B core antibody IgM, hepatitis B surface antigen, hepatitis C antibody, and blood cultures were negative. CRP was mildly elevated at 1.49. LDH was elevated at 469. EBV IgM and IgG were negative. Dengue fever antibody IgM was positive at 1.09 (interpretive criteria: <0.90 antibody not detected; 0.90-1.10 equivocal; >1.10 antibody detected).

The patient reported spontaneous improvement in her fevers and headache on follow-up within two weeks of her initial presentation.

Epidemiology

The number of dengue cases has been rising over the last two decades, and has become an increasingly important cause of febrile illness in travelers. Significant underreporting and a large percentage of asymptomatic disease confound reports of incidence and prevalence. Additionally, in the setting of increasing global mobility and international travel, there is increasing concern for wider spread of dengue and the establishment of autochthonous transmission in new geographic areas. The World Health Organization reported 3.2 million reports of dengue in 2015, which is an increase from 0.4 to 1.3 million in 1996-2005.[1] Global annual incidence is estimated at 50 to 100 million symptomatic cases, with the preponderance of cases being in Asia, Latin America, and Africa. Paralleling the increased global incidence of dengue, the number of dengue cases in returning travelers has been increasing steadily as well, such that dengue is now a more common cause of febrile illness than malaria in returning travelers from all tropical and subtropical regions, except Africa.[2]

The primary vector for transmission is the *Aedes aegypti* mosquito. There are four serotypes of dengue virus. While geographic distribution of the different serotypes varies, in recent years, most endemic countries report circulation of all four serotypes.[1] Infection with one dengue virus serotype induces long-lasting protection against that serotype, as well as temporary cross-protection against the other serotypes. Subsequent infection with a different serotype than the one that caused the primary infection may lead to more severe illness.

Clinical manifestations

Dengue can vary in clinical severity, ranging from undifferentiated fever, dengue fever with or without hemorrhage to dengue hemorrhagic fever with shock syndrome.[3] In children under the age of 15, the majority of infections do not manifest symptoms.[4] In adults, infections are usually associated with symptoms.[5] Classic symptoms of dengue include acute fever with headache, retro orbital pain, and muscle and joint pains. Symptom onset occurs about four to five days after an infected mosquito bite and the incubation can vary between three to fourteen days. The fever can last for five to seven days. About five percent of patients have a biphasic fever curve, with the second febrile phase lasting one to two days. After the fever, fatigue can linger for days to weeks in adults. A rash can occur two to five days after fever onset. For patients with a primary infection, development of rash is more common. Repeat infections are associated with higher level of symptoms and severity. Patients can experience more gastrointestinal (nausea, vomiting, diarrhea) and constitutional symptoms. Some patients may have cough, sore throat, and nasal congestion. Bleeding manifestations may also occur, most commonly from skin, nose, and gastrointestinal sites.

Dengue hemorrhagic fever is the most severe form of dengue virus infection and can be associated with circulatory failure and shock. It is associated with increased vascular permeability and hematologic changes. The plasma leakage develops between three to seven days after onset of illness, leading to pleural effusion, ascites, and hypotension, shock. Hematologic derangements include marked thrombocytopenia (< 100,000) and coagulopathy causing spontaneous bleeding or hemorrhagic tendency.[6] Dengue hemorrhagic fever can be differentiated from dengue fever by the following phases:

1) Febrile phase with high fevers.
2) Critical phase with plasma leak with development of pleural effusion, ascites. The plasma leak occurs as fever resolves and is manifested on labs as a sudden increase of the hematocrit > 20% of baseline, new onset leukopenia (< 5,000), hypoalbuminemia, and new hypocholesterolemia. The critical phase lasts 24-48 hours and management includes intravenous fluid administration as well as blood products as needed. Patients can develop oliguria, tachycardia and hypotension.
3) Convalescence phase with sudden cessation of plasma leak and reabsorption of fluids. Patients feel clinically improved with return of appetite, increased urine output, blood pressure stabilization. A convalescence rash develops (pruritic petechial rash with multiple round islands of normal skin). Changing intravenous fluid rate or cessation of fluid administration is important to avoid fluid overload.

No therapeutic agents are available to treat dengue infections. The mainstay of treatment is timely use of supportive care, including administration of fluids and close monitoring of clinical status.[7]

On physical examination, the findings are nonspecific. Twenty to fifty percent of patients have a macular or maculopapular rash, palatal petechiae, conjunctival injection, pharyngeal erythema, lymphadenopathy, and hepatomegaly. Leukopenia is common in adults and children. Thrombocytopenia can also develop, as well as elevation of AST two to five times the upper limit of normal.[8] Diagnosis is confirmed with use of serologic testing. An acute phase sample can be collected three or more days after onset of illness and an IgM immunoassay is used for rapid diagnosis. The IgM capture enzyme-linked immunosorbent assay (ELISA) is licensed for use in the USA. If the IgM immunoassay test is negative in the first six days of illness, testing for viral dengue RNA or NS1 antigen (nonstructural protein) can be obtained. Additionally, a RT-PCR assay was developed by the CDC for testing of dengue. In case of a negative acute phase test when there continues to be high suspicion of dengue infection, a convalescent test can be done with a hemagglutination inhibition (HI) assay or IgG ELISA.[9] The HI assay is not available in the US.

Prevention

Developing ways to reduce dengue virus infection and transmission both endemically as well as amongst travelers to endemic regions is important for reducing the morbidity and mortality associated with infection, as well as for potentially reducing the development of autochthonous transmission in new areas.

Currently, the burden of infection prevention lies in vector control and vector avoidance. Travelers should be counseled to use mosquito repellent containing DEET, stay in well-screened and air-conditioned buildings, and avoid outdoor exposure during times of prime mosquito activity.[10] Recently, vaccines against dengue virus have been in development. One vaccine is already registered for use in several countries (CYD-TDV, or Dengvaxia), and two others are currently in Phase III trials.[2] CYD-TDV contains four chimeric yellow fever 17D backbone viruses with premembrane and envelope proteins from each of the four dengue virus types replacing the same proteins in the yellow fever virus. It is administered at months zero, six, and twelve. Its efficacy ranges from 57-61% against virologically confirmed dengue of any severity caused by any virus type between 28 days and 13 months after the third vaccine dose.[2] During hospital-based surveillance, there was an increased risk of hospitalized dengue illness seen in children aged 2-5 years old during the third year after dose number one, but this signal disappeared among older age groups. One reason for this may be because the vaccine acts as a silent natural infection in seronegative children that then primes them to experience a secondary-like infection upon their first exposure to a true dengue infection.[2] For this reason, CYD-TDV is approved for ages 9-16 in endemic areas.

The WHO Strategic Advisory Group of Experts recommends CYD-TDV be introduced only in areas with high dengue endemicity (i.e. seroprevalence $\geq$ 70% in target age range).[10] For a dengue vaccine to perform well for use in travelers as

opposed to in endemic populations, several criteria will need to be accounted for. For example, the vaccine would need to ideally provide immunity against all four serotypes that is long-lasting, in order to avoid risk of a secondary-like infection that would cause more severe disease. Ideal candidate travelers would be those traveling frequently to dengue-endemic regions, to areas with epidemic dengue activity, or those who have had dengue in the past.[11] Additionally, ideally the vaccine series would be able to be completed more quickly without compromising efficacy, since the current CYD-TDV schedule of three doses over 12 months would likely be impractical for most short-term travelers.[11]

Conclusion

For travelers with febrile illness returning from tropical and subtropical regions, especially Asia, Central and South America, and the Caribbean, dengue should remain high on the differential. The severity of illness ranges from mild to severe, with severity often correlating with secondary infections with a distinct serotype of dengue virus than the initial infection. Mosquito prevention remains the mainstay of dengue prevention in travelers, but a vaccine for long-term immunity and protection remains on the horizon.

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