Yellow Fever in an Unvaccinated Traveler to Peru

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We present a case of an unvaccinated traveler who traveled from New York to Peru and contracted yellow fever. He likely acquired the infection while visiting the Amazon River, with a point of exit of Lima, Peru. Our case illustrates the dramatic course that yellow fever may take, as well as the importance of pretravel vaccination.

Keywords. urban transmission; yellow fever; yellow fever virus; zoonotic diseases.

Yellow fever (YF) is a mosquito-borne illness transmitted by the yellow fever virus (YFV), the prototypical member of the family *Flaviviridae* [1]. According to the Centers for Disease Control and Prevention (CDC), from 1970 to 2015, there have only been 10 cases of YF reported in unvaccinated travelers from the United States and Europe [2]. Given the high fatality rate in the intoxication stage of infection, as well as the lack of targeted treatments, vaccination remains the cornerstone of YF management. We report a case of YF in an unvaccinated traveler from New York to Peru.

CASE DESCRIPTION

A 74-year-old Caucasian male with a history of coronary artery disease and hypertension and no known prior liver disease presented to the emergency department (ED) with fever, chills, and jaundice. He had recently been on vacation in Peru, arriving there on October 6, 2016. He developed a fever of 101.4°F, nausea, and vomiting on October 14, 2016. He was treated for presumed gastroenteritis with antibiotics. However, he progressively got worse and was spiking daily temperatures. He developed watery diarrhea and abdominal pain. He was admitted to a local hospital, where stool antigen testing was positive for *Entamoeba histolytica*. There, he received ciprofloxacin and

metronidazole. Upon discharge, he continued to deteriorate and developed jaundice and confusion, so he returned to the United States on October 21, 2016, and presented from the airport to his local ED. During his stay in Peru, he visited Lima, Cuzco, and the Amazon River. He did not get YF vaccination. He drank 1–2 alcoholic beverages per week.

Upon arrival to the ED, he was vitally stable. His body mass index was 26.2. His sclera were icteric. His oral mucosa was pink and moist. The cardiopulmonary examination was normal. Abdominal exam revealed mild tenderness in right upper quadrant, with no guarding or rigidity. The liver was palpable just below the costal margin. The skin exam revealed marked jaundice with spider nevi across his chest. Cranial nerves II through XII were intact. He had normal tone and strength of extremities.

Initial blood work revealed a WBC count of 3.5 K/uL (with manual differentiation showing 57% segmental neutrophils, 13% bands, 8% lymphocytes, 7% atypical lymphocytes, 14% monocytes, and 0% eosinophils), hemoglobin of 15.9 g/dL, platelets of 53 K/uL, PTT of 49.4 s, INR of 1.48, Na of 135 mmol/L, K of 5.7 mmol/L, chloride of 97 mmol/L, bicarbonate of 10 mmol/L, BUN of 151 mg/dL, creatinine of 13.7 mg/dL (baseline 10 months prior noted to be 1.2 mg/dL), corrected calcium of 7.7 mg/dL, albumin of 3.4 g/dL, ALP of 349 U/L, AST of 3584 U/L, ALT of 3596 U/L, total bilirubin of 11.8 mg/dL, direct bilirubin of 6.7 mg/dL, CPK of 2297 U/L, and ammonia of 20 umol/L. Computed tomography (CT) of the abdomen/pelvis showed an enlarged and low-density liver, without any other acute findings. CT of the head and chest x-ray were normal.

Given his travel history, a related infection was considered, including YF, leptospirosis, typhoid fever, Q fever, Dengue, and viral hepatitis. He was admitted to the intensive care unit and started on ceftriaxone (for presumptive leptospirosis and typhoid fever), ciprofloxacin (for presumptive Q fever), and IVF.

On hospital day 2, he developed confusion with visual hallucinations. On hospital day 3, he developed a diffuse purpuric rash and melena and had a 4-gram drop in hemoglobin. Blood work was compatible with disseminated intravascular coagulation (DIC), with a PTT of 114 seconds, d-dimer of 2225 ng/mL, INR of 1.93, and fibrinogen of 104 mg/dL. That same day, he sustained a cardiac arrest, and after prolonged resuscitation, his family opted to withdraw care.

Postmortem gross examination revealed that the epicardial and endocardial surfaces of the heart, the liver, and both of the kidneys were yellowed. Microscopic analysis revealed subtotal hepatocellular necrosis with necrotic hepatocytes, intracellular cholestasis, and marked microvesicular steatosis

with a moderate inflammatory reaction. Tissue blocks of the liver were sent to the CDC for repeat analysis, which revealed fulminant active hepatitis with diffuse hepatocellular necrosis and cellular swelling, with numerous brightly eosinophilic apoptotic and necrotic hepatocytes with rounded contours and diffuse small and large droplet macrovascular steatosis. Immunohistochemical (IHC) assay for YFV demonstrated typical multifocal staining of necrotic hepatocytes throughout the lobules. The morphological features, together with the IHC staining pattern, were felt to favor infection with wild-type YFV, as opposed to vaccine-associated disease. This finding was in line with the patient's reported history. Polymerase chain reaction (PCR) testing was performed on RNA extracted from a tissue block, and the sequence analysis was compatible with wild-type YFV as well (YFV 5' noncoding region and YFV 3' untranslated region). Whole-genome sequencing was not performed, and so specific strain identification was not available.

Leptospira spp. real-time PCR, *Coxiella burnetii* IgM and IgG, Dengue virus real-time PCR, and acute viral hepatitis panel were negative. YF serology was unable to be sent and not completed postmortem. Bacterial blood cultures and stool cultures were negative.

DISCUSSION

YFV is highly virulent, and an infected mosquito is able to transmit up to 100 000 virus particles upon a single feeding [3]. This first stage of infection is the early viremic stage. If a patient is bit by a subsequent mosquito in this first stage of infection, they can then transmit those particles to the unaffected mosquito, thereby increasing the pool of disease-carrying vectors [3]. The second stage of infection is remission, during which patients will have a window period of improvement, and most will recover [1]. However, up to 25% of patients will progress to the intoxication stage, where their symptoms will recur and progress. This usually occurs around days 3–6, and as treatment is supportive, the fatality rate can be as high as 30–50% in this stage [1, 4].

In the early viremic stage, symptoms are often nonspecific and include fever, chills, nausea, and vomiting [5]. Our patient likely manifested these nonspecific symptoms, which were attributed to gastroenteritis. Common symptoms in the intoxication stage include high fever and hepatic dysfunction, but may also include renal, cardiac, and neurological abnormalities [6]. Hemorrhagic diathesis is also common due to decreased synthesis of vitamin K–dependent coagulation factors, platelet dysfunction, and DIC [3].

YFV has a narrow host range and is maintained in nature by cycling between nonhuman primates and mosquitoes [4]. Humans can become infected by 3 methods: via the sylvatic (or jungle) transmission cycle, whereby a human enters an endemic jungle area and is bitten by a viremic mosquito who previously fed on an infected primate; via the intermediate (or savannah) transmission cycle, where mosquitos transmit YFV to humans in jungle border areas; and via the urban transmission cycle, whereby humans are the primary reservoir [7]. In this cycle, humans infected with YFV who have high levels of viremia transmit the virus to domestic mosquitoes in densely populated urban areas. This feared cycle begins when a person travels to an endemic region and is bitten by an infected mosquito. They then travel to an urban area and, while viremic, transmit YFV to naïve mosquitos, which go on to infect further individuals.

Our patient visited Lima, Cuzco, and the Amazon River during his trip to Peru. Based on known prevalence data, he likely acquired the infection while visiting the Amazon River. In 2016, there were 80 cases of YF in Peru, of which 62 were laboratory proven, and 18 were considered probable [8]. These cases were geographically distributed among known at-risk regions, with no documented cases of YF occurring in the cities of Cuzco or Lima [8].

Vaccination is of the utmost importance, not only because it may prevent the deadly course that YF may take, but because of the possibility of urban transmission, which can lead to an epidemic. When a traveler visits an endemic region and acquires YFV, and then subsequently travels to a nonendemic region, they unwittingly may become the source of urban transmission. This was most recently documented in 2008 in Asuncion, Paraguay, when a traveler exposed in an area with sylvatic transmission led to an urban outbreak upon his return to the capital city [9]. There are currently limited published data available on the pretravel YF vaccination rates of travelers. Prior small-scale studies have documented variable rates, anywhere from 65–90% [10]. The true percentage may actually be far less, as some data suggest that only 35% of travelers to high-risk areas even seek medical travel advice [11]. Multiple countries in South America are not considered holoendemic for YF, including Peru, which makes preplanning all the more critical. A traveler may unwittingly enter an endemic area and not be aware of their potential exposure risk, as well as the threat of urban transmission.

CONCLUSION

YF is currently re-emerging on the global news front. As of December 2016, an outbreak of sylvatic YF is ocurring in Brazil, with 371 confirmed and 966 suspected cases as of March 2017 [12]. Conclusive data regarding YF vaccination rates are lacking, with variable reported rates in the literature. Keeping in mind the dramatic course that YF may take, the lack of targeted treatment therapy, and the overall effectiveness of the available vaccine [13], our case illustrates the importance of pretravel planning and adherence to recommended vaccination guidelines. Not only can individual fatalities be prevented, but the ever-present risk of urban transmission can decrease.

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