Imported Yellow Fever in a United States Citizen


The last imported case of yellow fever seen in this country was in 1924. We report a case of yellow fever acquired by an American tourist who visited the jungles of Brazil along the Rio Negro and Amazon Rivers. The patient died 6 days after hospital admission and 10 days after his first symptoms appeared. Yellow fever virus was recovered from clinical specimens, and the isolate was genetically similar to the E genotype IIB of South American yellow fever viruses. This patient’s illness represents a case of vaccine-preventable death since he failed to be immunized with a recommended preexposure yellow fever vaccine.

Yellow fever is a serious public health concern in many tropical countries in Africa and South America. There are two forms of transmission of the yellow fever virus. Most cases are acquired in rural areas (jungle yellow fever) where monkeys serve as the primary reservoir of yellow fever virus and the Haemogogus species of mosquito is the vector. In populated areas, person-to-person transmission can occur via the Aedes aegypti mosquito (urban yellow fever) [1].

From 1987 to 1991, there were more reported cases of yellow fever in areas of endemicity than during any other recorded 5-year period since 1948 [2]. Moreover, the A. aegypti mosquito has reinvested urban areas of South America and is present in much of the southeastern United States [3]. Areas involved included Texas, nine southeastern states, and the territories of Puerto Rico and the Virgin Islands. These factors in addition to heavy air traffic between the southeastern United States and areas of endemicity in South America make possible a future outbreak in the United States [2, 3]. Medical history from decades ago supports the concern that yellow fever could pose a serious public health risk in this country [2].

The last imported case of yellow fever in the United States was reported in 1924 [4]. We therefore present a case of imported jungle yellow fever acquired by a Tennessee resident who visited the jungles of Brazil along the Rio Negro and Amazon Rivers in August 1996. He had neglected to be immunized with a recommended preexposure yellow fever vaccine before leaving the United States.

Case Report

A 45-year-old man returned from a 9-day trip to Brazil with headache, myalgia, joint pains, and chills. He was first treated as an outpatient with intravenous fluids and pain medications that relieved his symptoms. At that initial emergency department visit, he had a temperature of 39°C, leukopenia, mild thrombocytopenia, and an elevated glutamic-oxaloacetic transaminase level (table 1). There was no evidence of bleeding. Because of the patient’s recent travel history, dengue was included in the differential diagnosis as a cause of the patient’s illness, and he was discharged to be followed up as an outpatient.

He returned 3 days later with recurrence of headache and new complaints of nausea, vomiting, epigastric pain, and dizziness. No hematemesis was reported. Physical examination revealed an ill-appearing patient with a temperature of 38.6°C; blood pressures of 102/74 mm Hg and 80/50 mm Hg supine and standing, respectively; pulse rate of 92; and respiration rate of 16. He had icteric sclerae, a supple neck, an enlarged liver measuring 3 cm below the costal margin, and tenderness in the epigastrium. Results of his neurological examination were normal, and he had several skin lesions on his extremities that were caused by recent insect bites. The leukopenia was more severe, and he had developed thrombocytopenia and laboratory evidence of marked hepatic and renal dysfunction (table 1).

He was hospitalized in a critical care unit with a preliminary diagnosis of viral hemorrhagic fever of undetermined origin and treated with broad-spectrum antibiotics and granulocyte colony-stimulating factor. Ribavirin was empirically administered to treat a possible South American arenavirus infection, although yellow fever was considered the most likely cause of the patient’s illness. Multiple blood, sputum, and urine cultures were negative for bacterial pathogens. Examination of two malaria smears of peripheral blood showed no parasites, and titters...
### Table 1. Early laboratory findings for a United States resident with imported yellow fever.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Outpatient visit (11 August 1996)</th>
<th>Hospital admission (14 August 1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral leukocyte count (/mm³)</td>
<td>3,200</td>
<td>1,400</td>
</tr>
<tr>
<td>Hemoglobin level (g/dL)</td>
<td>14.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Platelet count (/mm³)</td>
<td>131,000</td>
<td>72,000</td>
</tr>
<tr>
<td>Sodium level (mEq/L)</td>
<td>134</td>
<td>127</td>
</tr>
<tr>
<td>Potassium level (mEq/L)</td>
<td>3.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Blood urea nitrogen level (mg/dL)</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>Creatinine level (mg/dL)</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Alkaline phosphatase level (U/L)</td>
<td>35</td>
<td>12,258</td>
</tr>
<tr>
<td>Glutamic-oxaloacetic transaminase level (U/L)</td>
<td>214</td>
<td>19,025</td>
</tr>
<tr>
<td>γ-Glutamyltransferase level (U/L)</td>
<td>34</td>
<td>154</td>
</tr>
<tr>
<td>Total bilirubin level (mg/dL)</td>
<td>0.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>ND</td>
<td>26.2</td>
</tr>
<tr>
<td>D-Dimer level (μg/mL)</td>
<td>ND</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>ND</td>
<td>82</td>
</tr>
<tr>
<td>Fibrinogen level (mg/dL)</td>
<td>ND</td>
<td>107</td>
</tr>
</tbody>
</table>

**NOTE.** ND = not determined.

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### Virological Studies

#### Materials and Methods

**Isolation of virus from clinical specimens.** Four clinical specimens (whole blood, serum, liver tissue, and liver tissue in a viral transport medium consisting of veal infusion broth and gelatin) were inoculated onto Vero, C6/36, and AP-61 cells in tissue cultures and also intracerebrally into 2-day-old suckling mice. Whole blood and serum specimens were obtained before death on the 10th day of illness; liver specimens were obtained during postmortem examination. No cytopathic effect was observed in any of the tissue cultures. The mice remained healthy through 1 month of daily observations. Direct fluorescent antibody testing for the presence of flavivirus on tissue culture cells harvested on day 10 revealed that only whole blood inoculated onto AP-61 cells was positive. Less than 1% of the cells showed fluorescence.

**Virus gene sequencing and phylogenetic analysis.** Viral RNA was extracted directly from a virus preparation of a medium from cultured AP-61 cells or a 10% suspension of suckling mouse brain as previously described [5]. Yellow fever virus–specific oligonucleotides used in reverse transcriptase-PCR amplification of viral RNA and sequencing of the E gene were the same as those previously described [6]. Double-stranded PCR-amplified DNA sequences from multiple amplification reactions were purified by using a GeneClean II kit (BIO 101, Vista, CA). Sequencing reactions were performed by means of Taq DyeDeoxy Terminator cycle sequence kits (Applied Biosystems, Foster City, CA).

Nucleotide acid and protein sequence analysis was determined by using the computer program HIBIO DNASIS/PROSIS (Hitachi Software Engineering, Brisbane, CA). The phylogenetic relationship of the Tennessee yellow fever 1996 (TNYF96) virus isolate with other yellow fever virus isolates was constructed by means of the program Molecular Evolutionary Genetic Analysis version 1.01 (Pennsylvania State University, University Park, PA). Significance of the phylogenetic trees was subjected to statistical bootstrap analysis with 500 replicas.

### Results

**Viral identification.** Indirect fluorescent antibody tests of the isolate from AP-61 cells in tissue culture were positive for monoclonal antibody (mAb) 5E3 to all yellow fever viruses and mAb 4G2 to all flaviviruses. The isolate was inoculated again into AP-61 cells and into suckling mice. The mice were sick on day 7. The cells were harvested on day 8, and indirect fluorescent antibody tests were completed. Additional results were as follows: mAb 864 (specific to the vaccine strain of yellow fever virus 17D) did not react with the isolate at dilutions of 320 to 10,240, and MAB 117 (specific to wild-type yellow fever virus) [7] had a positive reaction at dilutions from 1:80 to 1:1,280. These indirect fluorescent antibody tests were repeated with the same results. Controls included yellow fever of IgM and IgG antibodies to *Leptospira* in serum were not elevated.

He developed disseminated intravascular coagulation (DIC) and confusion on the second hospital day; his condition deteriorated rapidly, and he required intubation to maintain his airway. A lumbar puncture was done, and findings of CSF analysis were normal. He developed active bleeding from gastrointestinal, oropharyngeal, and central venous catheter sites. Numerous transfusions of blood products, including 38 units of fresh frozen plasma and 28 units of platelets and antithrombin III, failed to stop the bleeding. In addition, low-dose administration of heparin was unsuccessful in reversing DIC. Ultimately, he received 25 units of packed RBCs. The patient died 6 days after hospital admission and 10 days after the onset of symptoms.

### Postmortem Examination

Autopsy was limited to thoracic and abdominal viscera to limit exposure time and avoid aerosolization produced by an electric saw. Multiple areas of petechiae and ecchymoses were seen in the skin, heart, liver, and kidneys that were consistent with a DIC-like syndrome.

The liver weighed 2,000 g, was pale yellow in color, and had a greasy texture. Microscopic examination of the liver demonstrated massive midzonal necrosis with single layers of viable perportal and pericentral hepatocytes. In some areas, the pericentral hepatocytes were also necrotic. Inflammatory infiltrates were absent, and fatty degeneration was diffuse and severe.
virus Asibi, yellow fever virus 17D, a recent isolate from the Ivory Coast, and normal control cells. On these indirect fluorescent antibody slides, 50% of the cells were infected.

**Virus gene sequencing and phylogenetic analysis.** Comparison of sequences of E gene from the TNYF96 virus with those from 20 other previously reported yellow fever viruses revealed similarities of nucleotide sequences of 8.0% to 80.0%. The TNYF96 virus had the highest sequence similarity with the Trinidad, Brazil, and Colombia isolates (98.0%, 97.0%, and 96.2%, respectively) [6]. The monophyletic grouping of these four viruses was also observed in 100% of the statistical bootstrap analysis. It indicated that the TNYF96 virus was genetically similar to the E genotype IIB of South American yellow fever viruses [6].

**Discussion**

Severe yellow fever includes the three clinical periods of infection, remission, and intoxication, which were displayed by our patient’s clinical course [8]. The period of infection lasts ~3 days and begins suddenly with headache, malaise, weakness, nausea, and vomiting. In this period, the virus is present in high titers in the blood, and the patient may become a source of infection for mosquitoes. During the period of remission, fever and symptoms disappear for ~24 hours but then return. Jaundice, albuminuria, oliguria, cardiovascular instability, and hemorrhage are seen in the period of intoxication. Hemorrhagic manifestations became prominent in our patient and included active bleeding from multiple sites with evidence of DIC. Delirium, seizures, coma, and other CNS signs can be present in the intoxication stage and are considered “preterminal.” In the case presented here, most of these findings manifested in a characteristic sequence.

Mortality rates associated with severe yellow fever are variable; these rates have been reported to be as high as 50% [8, 9], but in a yellow fever epidemic, they can be as low as 5% [10]. Mortality rates are increased among patients who exhibit jaundice [1], which was seen in our patient.

Complications of yellow fever are similar to those of other viral hemorrhagic fevers but are often associated with more severe hepatic involvement [8]. Microscopic analysis of liver tissue specimens from patients with yellow fever shows necrosis of the midzone with sparing of the central veins and portal triads [8, 11]. Councilman’s bodies (which are intensely eosinophilic, necrotic hepatocytes) and fatty changes are frequently noted [8, 11, 12]. A diagnosis of yellow fever can be made on the basis of findings of histopathologic examination of the liver [11, 12], but these pathognomonic histopathologic changes are seen only during the acute phase of illness. Later, in the clinical course, hepatic transformations often resemble nonspecific massive necrosis [12]. Examination of liver specimens obtained from our patient during autopsy demonstrated the classic findings of midzonal necrosis with sparing of hepatocytes surrounding the central veins and portal triads as well as Councilman’s bodies and fatty metamorphosis. Although not validated in the clinical setting, newer methodologies based on nucleic acid amplification have been described [13, 14] that could result in rapid diagnostic testing of yellow fever in the future.

Current therapy for yellow fever is supportive and includes treatment of hemorrhage, shock [8], and hepatic dysfunction. Nasogastric suction and intravenous histamine-2 blockers have been used to reduce the risk of bleeding. Controversy exists in the treatment of coagulopathy associated with yellow fever. Transfusions with fresh frozen plasma have been recommended to keep the prothrombin time between 25 seconds and 30 seconds [8] in patients without active bleeding. Administration of heparin is thought to decrease the severity of bleeding in patients with DIC associated with yellow fever [3]. In humans and monkeys, ribavirin has been shown to be of therapeutic benefit as treatment of viral hemorrhagic fevers caused by the Lassa fever virus [15, 16], but it has not been of proven benefit as treatment of or prophylaxis for yellow fever [16]. Plasmapheresis [17] and liver transplantation [18, 19] have been used in the management of fulminant liver failure in patients with illnesses other than yellow fever; these were not considered treatment options for our patient because of his severe refractory DIC and uncontrollable bleeding. Despite years of research, the best treatment of yellow fever remains prevention with preexposure vaccination.

Yellow fever is known to be transmitted by a mosquito bite or through experimental or accidental inoculation of blood from a patient with yellow fever, as demonstrated by the classic studies by Reed et al. in 1901 [20]. Our patient had numerous opportunities for exposure to infected mosquitoes. His activities included wading in rivers and fishing and sleeping on a boat. His tour group observed monkeys on one occasion from 100 to 200 yards away.

One case of transmission of yellow fever to a health care worker has been reported [21]. A laboratory technician who performed phlebotomy on a patient with yellow fever in 1930 and apparently had no abrasions on his hands and no history of a needlestick developed yellow fever. The patient survived, but the technician died of complications of yellow fever. Nosocomial transmission of our patient’s illness (which was undefined at that time) was of concern during his hospitalization, especially since he required multiple invasive procedures and skilled critical nursing care. A limited autopsy was performed with restricted personnel because possible transmission of an infectious agent was a strong consideration.

The *A. aegypti* mosquito is found in the southeastern United States; epidemiologically, this sets the stage for a possible future outbreak of yellow fever in this area [2, 3]. Outbreaks of yellow fever have been well described in the southeastern United States in the past [22]. Our patient could have been a source of an outbreak of yellow fever since he traveled through the southeastern United States at a time when he was infectious and mosquito activity was present.
The Pan American Health Organization led vector control programs in the 1950s and 1960s and reduced significantly or eliminated *Aedes* infestations in most countries in the Americas. The programs for *A. aegypti* eradication have not been continued in many countries, and the mosquitoes have reinfested all Latin American countries except Chile and Uruguay [23]. Increasing numbers of cases of dengue and yellow fever have been documented since the mid-1980s [2, 23].

Vaccination against yellow fever is recommended for persons traveling in areas of endemicity and should be obtained 7 to 10 days before travel to ensure immunity [9]. Seroconversion is achieved in 95% of vaccine recipients [24]. Some countries require evidence of vaccination against yellow fever for all travelers, and other countries require evidence of vaccination only for those travelers coming from areas of endemicity. They may waive the requirement for vaccination if the traveler is from a noninfected area and is staying in the area of endemicity for <14 days [25]. Brazil has required vaccination against yellow fever for travelers who are coming from an area of endemicity and are older than 9 months of age. There are no vaccination requirements for international travelers entering the United States [25].

Our patient was seen by his primary care physician for travel-related medical recommendations. He received hepatitis A vaccine, immune serum globulin, and a prescription for prophylaxis for malaria, which he subsequently took. Vaccination against yellow fever was recommended but not available at his physician’s clinic. A health department clinic located 25 miles from his residence was the closest clinic offering vaccination against yellow fever; he never received the yellow fever vaccine.

Vaccination against yellow fever in the United States is limited to designated centers [26]. These health care facilities agree to meet specific requirements in all aspects of administration of yellow fever vaccine including transport, handling, and storage of the vaccine available in the United States (which contains a highly temperature-sensitive attenuated virus that must be kept at 0°C–5°C during transportation and storage). In addition, the vaccine must be used within 60 minutes once it is reconstituted.

Immunity to yellow fever in travelers to areas of endemicity is a concern not only for protection of individuals but also for prevention of possible epidemics [22, 27]. A recent European traveler to South America who was not immunized returned home and subsequently developed yellow fever [28]. It was speculated that this Swiss tourist probably became infected during a short boat trip near Manaus, Brazil. It is noteworthy that our patient also traveled by boat near Manaus.

The type of exposure, incubation period, clinical course, histopathologic findings, and viral culture with viral genetic analysis prove that the present case represents the first one of imported yellow fever seen in this country in >70 years. Our patient’s illness serves as a grim reminder that vaccine-preventable deaths continue to occur despite the availability of safe and effective vaccines. In this case, the vaccine was not readily available at the patient’s local physician’s office since it was not a certified site for administration of yellow fever vaccine. The lack of recommended vaccination in this case not only was directly related to our patient’s death but also served as a risk factor for reintroducing epidemic yellow fever into the southeastern United States.

References


