A Belgian Traveler Who Acquired Yellow Fever in The Gambia

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A 47-year-old Belgian woman acquired yellow fever during a 1-week vacation in The Gambia; she had never been vaccinated against yellow fever. She died of massive gastrointestinal bleeding 7 days after the onset of the first symptoms. This dramatic case demonstrates that it is important for persons to be vaccinated against yellow fever before they travel to countries where yellow fever is endemic, even if the country, like The Gambia, does not require travelers to be vaccinated.

World Health Organization (WHO) data suggest that the rate of yellow fever transmission is increasing, especially in sub-Saharan Africa. The WHO estimates that, after adjustment for underreporting, ~200,000 cases of yellow fever occur each year [1, 2]. In most of west Africa, with the exception of The Gambia, yellow fever vaccination coverage is low, and there are regular epidemics of yellow fever that fluctuate according to the sylvatic cycle. Since the mid-1990s, epidemics have been reported from Ghana, Gabon, Liberia, Senegal, Benin, and Ivory Coast [3].

We report a case of yellow fever in a Belgian traveler who acquired this infection in The Gambia. Before this case was encountered, the most recent documented case of yellow fever from The Gambia had been diagnosed in 1979 [4].

Case report. On 1 November 2001, a 47-year-old Belgian woman and her 13-year-old son arrived in The Gambia for a 1-week vacation. They had taken a direct flight from Brussels, Belgium, to Banjul, The Gambia. Neither the mother nor her son had ever been vaccinated against yellow fever, despite the fact that the mother had traveled to Venezuela in 1998. She had only been advised by her general practitioner to take chloroquine and proguanil as prophylaxis for malaria. When the woman was 20 years old, she had Crohn disease diagnosed, and in 1996, a colostomy had been performed because of multiple abdominal abscesses.

During their 7 days in The Gambia, the woman and her son stayed at a tourist hotel in Bakau. From there, on 2 November, they visited the localities of Serekunda, the Bintang Bolong mangrove, and Brikama town with a local guide. On 3 November, they remained at the hotel in Bakau. On 4 November, they visited the Abuko nature reserve; on 5 November, they visited Tanji (a village of fishermen), the Tanji bird reserve, and Gunjur; and on 6 November, they visited Barra.

On the evening of 7 November, the mother became acutely ill, with a very high temperature, chills, frontal headache, back pain, muscle pain, and asthenia. On 8 November, the woman and her son returned by direct flight from Banjul to The Netherlands. During the flight, she felt very weak and complained of a sore throat. On 9 November, she developed diarrhea, but without blood or mucus in the stool, and she complained of nausea and severe asthenia.

On 10 November, the woman was admitted to the intensive care unit of the Clinic St.-Pierre (Ottignies, Belgium) because of high fever, severe headache, lower back pain, muscle pain, discrete jaundice, and severe asthenia. She had almost complete anuria. For the 3 days before hospitalization, she had been receiving amoxicillin and acetaminophen. Physical examination revealed a body weight of 49 kg (height, 1.59 m), a temperature of 35.6°C, blood pressure of 120/80 mm Hg, and a pulse of 60 beats/min. There were no signs of bleeding, and the findings of a neurological examination were normal. Laboratory tests performed at the time of admission to the hospital revealed the following values: hemoglobin, 12.8 g/dL (normal range, 12–17 g/dL); hematocrit, 35.5% (normal range, 38%–52%); platelet count, 95,000 platelets/mm^3 (normal range, 150,000–450,000 platelets/mm^3); leukocyte count, 4100 cells/mm^3 (normal range, 4800–10,800 cells/mm^3); creatinine, 6.9 mg/dL (normal range, 0.4–1.4 mg/dL); blood urea nitrogen, 151 mg/dL (normal range, 15–55 mg/dL); potassium, 4.8 m*M* (normal range, 3.5–5.5 m*M*); alkaline phosphatase, 228 U/L (normal range, 32–122 U/L); aspartate aminotransferase, 49,000 U/L (normal level, <34 U/L); alanine aminotransferase, 23,000 U/L (normal level, <44 U/L); total bilirubin, 3.5 mg/dL (normal level, <1.2 mg/dL); direct bilirubin, 2.5 mg/

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L (normal level, <0.5 mg/dL); prothrombin time, 26% (normal range, 70%–100%); international normalized ratio, 3.3 (normal range, 0.9–1.3); ammonia, 64 μg/dL (normal level, <100 μg/dL); and C-reactive protein, 13.8 mg/dL (normal level, <1 mg/dL). The findings of chest radiography, ultrasound examination of the abdomen, CT of the brain, and electrocardiography were all normal.

On 11 November, a slight conjunctival injection and enanthem of the palate was noted. The patient felt pain on palpation of the right hypochondrium and muscles. She was very asthenic, but neurological findings were normal. She remained anuric, and hemodialysis was started because of hyperkalaemia.

At 4:00 A.M. on 12 November, the diagnosis of yellow fever was confirmed by RT-PCR performed by the Department of Virology, Bernard Nocht Institute of Tropical Medicine (Hamburg, Germany). The plasma sample initially tested negative for yellow fever because of the presence of PCR-inhibiting activity. This inhibition could be reversed by dilution of the sample at a ratio of 1:100 before extraction of nucleic acid. The virus was still detectable at this dilution. Quantitative PCR of the undiluted plasma sample yielded a virus load of $>10^6$ copies/mL.

The patient's coagulation status was now seriously impaired, the prothrombin time was very low (17%), and the international normalized ratio was 5.1. She started to bleed from the injection sites, and red blood was observed in the colostomy bag. The patient developed hypovolemic shock.

On the afternoon of 13 November, a certain degree of slowness of speech was noted, but consciousness remained normal and there was no flapping tremor. Because liver transplantation was considered, the patient was transferred to the intensive care unit of St.-Luc Hospital (Brussels). During transportation, she developed status epilepticus. She was treated with diazepam and underwent intubation and ventilation.

At the time of admission to St.-Luc Hospital, the patient's blood pressure was 110/50 mm Hg, and supraventricular tachycardia (pulse, 187 beats/min) was noted. A chest radiograph revealed signs of pulmonary edema. A new CT scan of the brain did not reveal any abnormalities. Electroencephalography findings were compatible with grade II hepatic encephalopathy. The ammonia level had increased to 216 μg/dL. The patient's factor V level was low (16%; normal range, 70%–110%). Highly purified neutralizing murine antibodies (provided by the Robert Koch Institut, Berlin, Germany), which are capable of protecting mice from infection, were administered to the patient, but there was no clinical improvement. She started vomiting altered blood in large quantities. She underwent transfusion with 6 U of fresh frozen plasma, 4 U of RBCs, 4 U of platelets, and 2 U of pasteurized protein solution (4% albumin), but her hemodynamic situation did not improve. She remained comatose and developed hypothermia. Laboratory tests revealed severe metabolic acidosis (pH, 7.16; normal range, 7.35–7.45) with a high level of lactic acid (9.6 m*M;* normal range, 0.9–1.7 m*M*).

The patient finally died at 6 A.M. on 14 November 2001. A postmortem examination confirmed that she had died while experiencing shock because of massive gastrointestinal bleeding. Her 13-year-old son never developed any symptoms of yellow fever, and the results of a PCR test for yellow fever performed with a serum sample obtained on 10 November were negative.

Discussion. There are several lessons to learn from this dramatic case. The most important one is that travelers should be vaccinated against yellow fever when they travel to countries where it is endemic, even if the country does not require travelers to be vaccinated. Yellow fever remains endemic in west Africa. Even urban yellow fever has recently been detected in Abidjan, Ivory Coast [5]. Many countries in areas of endemicity in Africa (such as The Gambia) and South America (such as Venezuela) do not require travelers to undergo yellow fever vaccination. International guidelines for travelers recommend vaccination against yellow fever for persons traveling to these countries [6], but general practitioners and travel agencies may advise against vaccination, because such vaccination is not required by the countries themselves.

So far, only a limited number of travelers have acquired yellow fever after returning from South America or Africa [7–13]. Since 1924, there have been only 3 imported cases of yellow fever in the United States. During 1996–2002, 5 fatal cases of yellow fever occurred in unvaccinated travelers from the United States [8–10] and Europe [11, 12]. These infections were acquired in Brazil (3 cases) [8, 10], Venezuela [9], and Ivory Coast [12]. In 1987, a 37-year-old Spanish woman developed yellow fever despite having been vaccinated 5 years earlier [13]. She recovered from the disease. It was suggested that, for this woman, the vaccination failure may have been related to a problem associated with storage of the yellow fever vaccine. Indeed, this vaccine should be stored at a temperature of <4°C.

In contrast with the case we report, in most imported cases of yellow fever, the diagnosis has not been suspected initially. A patient who was hospitalized in 1999 in Germany was initially considered to have Lassa fever or even Ebola hemorrhagic fever, because the patient incorrectly claimed to have been vaccinated against yellow fever [12]. This caused a lot of panic and use of unnecessary measures, such as transfer of the patient to a negative-pressure isolation unit, quarantine of close contacts, and tracing of all possible contacts, including the passengers of an airline flight. In the case of our patient, only the simple measures of avoidance of contact with blood and body fluids were advised.

The clinical manifestations of disease noted in our patient

were characteristic of yellow fever. She was probably infected during the first days of her stay in The Gambia (the incubation period of yellow fever is generally 3–6 days) [2]. Her illness started very acutely, with high temperature, headache, muscle pain, and asthenia. The fever disappeared after 4 days of illness, but, during a second phase of illness, the patient developed extensive gastrointestinal bleeding and shock. Of patients with hepatorenal disease caused by yellow fever, 20%–50% typically die 7–10 days after onset [2].

The traditional dogma in military circles has been that, if at all possible, patients with viral hemorrhagic fever should be treated where they lie, because the combination of vascular instability and leaky capillary syndrome results in an increased risk of hemorrhage during transportation. During transportation, our patient developed status epilepticus, but this was probably caused by hepatic encephalopathy. Our patient died in the second hospital to which she was admitted, 13 h after admission, because of massive gastrointestinal bleeding. It is clear that we should try to avoid the transportation of patients with viral hemorrhagic fever, but we do not believe that transportation of our patient influenced the outcome.

Another lesson learned from this case is that international networks, such as the European Network for the Diagnostics of "Imported" Viral Diseases (ENIVD), can be extremely helpful for establishing early etiological diagnosis of viral hemorrhagic fever. Such an early diagnosis is necessary to take essential steps—not only treatment of the patient but, also, instigation of appropriate measures to avoid the transmission of more-infectious causes of hemorrhagic fever, such as Ebola virus, Marburg virus, Crimean-Congo fever virus, and Lassa fever virus.

As soon as the clinical diagnosis of yellow fever was confirmed, Belgian health authorities, the WHO, and health authorities in The Gambia were alerted. In The Gambia, a surveillance system for yellow fever was organized, but, so far, no excess of cases of jaundice has been reported. A survey performed in December 2000 in the western region of The Gambia showed that yellow fever vaccine coverage in 12–23-month-old subjects was 88% (95% CI, 85%–91%; P. Milligan, personal communication). However, it is likely that certain forest monkeys and *Aedes* mosquitoes in The Gambia are infected. In neighboring Senegal, cases of yellow fever have recently been diagnosed [14]. In The Gambia, at the Abuko nature reserve and in the mangrove area frequented by tourists, forest monkeys are a common sight, and they wander freely on the paths of the Abuko reserve and may even try to pick the pockets of tourists. Our patient reported that she had given food to a monkey at the Abuko nature reserve. Our patient visited The Gambia at the end of an unusually prolonged and warm wet season—conditions that are highly favorable for mosquitoes.

Yellow fever vaccine is regarded as one of the safest attenuated virus vaccines, with few associated side effects or adverse events [2]. However, cases of hemorrhagic fever associated with yellow fever 17D substrain vaccination have recently been reported from Brazil (2 cases, both of which were fatal) [15], the United States (4 cases, 3 of which were fatal) [16], and Australia (1 fatal case) [17]. Three other cases (2 of which were fatal) were not described in detail in the literature [18]. These reports have raised concerns about the safety of the vaccine and the mechanisms that cause fatal disease in certain individuals. However, because yellow fever remains an important cause of illness and death in tropical South America and Africa, vaccination of local populations and persons traveling to these areas remains highly recommended [19]. Yellow fever vaccination has to be given $\geqslant$10 days before a person leaves for an area where yellow fever is endemic [2]. It is clear that many people (particularly last-minute travelers) are not vaccinated adequately [20]. In a survey of persons who went on business trips to Nigeria at the moment that a yellow fever epidemic was underway in that country, it was found that 15 (22%) of the business travelers received yellow fever immunization <10 days before they left for a yellow fever zone, compared with 9 (8%) of persons who traveled there on holiday [20] In conclusion, all travelers to countries in Africa and South America where yellow fever is endemic should be vaccinated, even if they are only visiting large cities [21] or countries with high coverage of yellow fever vaccination, such as The Gambia.

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