

Case Report: A Case of Yellow Fever Vaccine–Associated Viscerotropic Disease in Ecuador

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Abstract. We report the first case of viscerotropic syndrome in Ecuador. Because of similarities between yellow fever and viscerotropic syndrome, the incidence of this recently described complication of vaccination with the 17D yellow fever vaccine is not known. There is a large population in South America that is considered at risk for possible reemergence of urban yellow fever. Knowledge of potentially fatal complications of yellow fever vaccine should temper decisions to vaccinate populations where the disease is not endemic.

Yellow fever is a viral hemorrhagic fever currently encountered in tropical regions of Africa and the Americas. The habits of the mosquito vectors that transmit yellow fever determine how yellow fever behaves in epidemics. In South America, sylvatic yellow fever is a zoonosis that occurs when tree-dwelling mosquitoes transmit the virus from an epizootic among monkeys to humans, and is usually manifested by sporadic, isolated cases.¹ Urban yellow fever can emerge in dramatic epidemics when the virus is transmitted from human to human by *Aedes aegypti*, the same mosquito that transmits dengue. Urban yellow fever had been eliminated from South America by vector control in the early 20th century, but control of *A. aegypti* has decreased, and reemergence of urban yellow fever was documented recently in Paraguay where a group of persons who acquired sylvatic yellow fever returned to their home in an area with a high index of *A. aegypti* infestation.² There is now a large population thought to be vulnerable to the possible reemergence of urban yellow fever in South America. Persons in some of the areas where urban yellow fever had been eradicated in the past century are now being vaccinated against yellow fever.³

The yellow fever vaccine has been reputed to be one of the safest vaccines produced and has saved many lives. All vaccines now in use have been derived from the 17-D strain, an attenuated strain that was found by serial passage through animal and cell culture. Since 1947, a seed lot system has been used for vaccine production in an effort to reduce the possibility of further mutations that might change the safety profile of the vaccines.⁴ Vaccination typically produces a mild viremia 3–7 days after vaccination and has been associated with headache, myalgia, and slight fever in 25% of vaccine recipients.

Serious adverse effects of the yellow fever vaccine include anaphylaxis and neurotropic and viscerotropic complications. Yellow fever vaccine–associated neurotropic illness has been known since the formulation of the vaccine and has resulted in the suspension of use of a vaccine made in France. Most persons affected with this illness recover. Since 1996, a rare syndrome has been described in which the vaccine causes a febrile multisystemic illness called the yellow fever–associated viscerotropic syndrome, which has a high mortality rate. This report describes the first case of this syndrome in Ecuador.

A 67-year-old man was admitted to Hospital Vozandes in Quito, Ecuador, in November 2008, with a five-day history of a

febrile illness, headache, severe abdominal pain, anxiety, nausea and vomiting, dyspnea, jaundice, leucopenia, and thrombocytopenia. His symptoms started three days after receiving a yellow fever vaccine and became progressively worse. The eastern rain forest of Ecuador is endemic for sylvatic yellow fever. Panama requires that persons with passports from countries with endemic yellow fever show evidence of yellow fever vaccination in the last 10 years. He received the vaccine in preparation for a tourism trip to Panama City, Panama. Prior medical history was not remarkable except for weekly alcohol intake to the point of intoxication. The patient did not take medicines aside from acetaminophen and a combination of ergotamine and lysine used for headaches.

On admission, his blood pressure was 110/70, and he had a pulse rate of 72 beats/minute, a respiration rate of 20/minute, a temperature of 36°C and an oxygen saturation rate of 74% on room air. After blood and urine cultures, he was given ceftriaxone and intravenous hydration. Three hours after admission, he was transferred to an intensive care unit because of multiorgan system failure and was given intravenous pressors, hydrocortisone, vancomycin, and cefepime. On the second day in the hospital, oliguric renal failure developed. Results of computed tomography of the abdomen were unremarkable. A bone marrow biopsy specimen showed myeloid arrest with plasmacytoid atypical lymphocytes. On the third day in the hospital, a cardiac arrhythmia developed, the patient did not respond to cardiopulmonary resuscitation, and he died. An autopsy showed pulmonary edema.

All cultures of blood, urine, and tissues were negative for bacteria. Tissue biopsy specimens obtained in the autopsy were placed in formalin, frozen and then embedded in paraffin; freezing caused artifacts to develop. The paraffin blocks of tissue were sent to the Centers for Disease Control and Prevention (Atlanta, GA). An immunohistochemical test was performed by using an indirect immunalkaline phosphatase technique.⁵ The primary antibody was a mouse anti-yellow fever antibody. Yellow fever virus was detected in heart, liver, and spleen, but not in the lung or kidney. RNA was extracted from the formalin-fixed, paraffin-embedded tissues, and a flavivirus-specific reverse transcription–polymerase chain (RT-PCR) reaction specific for the non-structural protein 5 gene was performed. Sequence analysis of 250-basepair amplicons showed 98% homology with the yellow fever vaccine (strain 17D-Brazil). A parallel RT-PCR amplification of 18S ribosomal DNA was also successful, ensuring that amplifiable host nucleic acid was extracted. This case-patient was reported to the Ecuadorian Ministry of Public Health. The presence of yellow fever virus antigens and nucleic acids in heart, liver, and spleen; the chronology of receipt of the vaccine;

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and the clinical picture of multiorgan failure are all indicative of a viscerotropic yellow fever virus infection caused by the vaccine virus.

Yellow fever vaccine-associated viscerotropic disease has been defined as a febrile illness that begins 3–5 days after vaccination and clinically resembles naturally acquired yellow fever.⁶ Although a retrospective study reported a case as early as 1975,⁷ yellow fever-associated viscerotropic syndrome was not recognized until 1996, and the name was given to it in 2002.⁸ By March 2007, 36 cases of yellow fever vaccine-associated viscerotropic disease were reported.⁹ Four additional cases were reported in Peru in 2008.³ Munoz and others reported a case in May 2008 in Spain.¹⁰ Our study identifies the first report of viscerotropic disease in Ecuador.

Illness similar to yellow fever that occurs in persons vaccinated in enzootic regions has been confused with natural infection.¹¹ Most deaths caused by yellow fever occur before the patient has mounted an immune response and after most of the virus has disappeared from the blood, making it difficult to confirm yellow fever in areas where sylvatic yellow fever cases are sporadic and resources are limited.¹ If this patient had been in an area endemic for yellow fever, his illness might have been attributed to wild-type virus instead of vaccine virus. Without the chronologic history of the vaccine, this case would have been diagnosed as sepsis without an identified cause and would not have been considered to be yellow fever. Illness in persons outside enzootic regions, such as this case, can easily be confused with septic shock.

Because of difficulties in recognizing this syndrome, it is difficult to estimate the true incidence of yellow fever-associated viscerotropic syndrome. Martin and others reviewed data from the U.S. Vaccine Adverse Event Reporting System from 1990 through 1998 and reported a rate of serious adverse events (SAEs) excluding anaphylaxis of 2.43 reactions/100,000 persons for all age groups and 5.8 events/100,000 persons for persons more than 65 years of age.¹² Lindsey and others reviewed data from the same system from 2000 through 2006 and reported a rate of SAEs of 1.2 events/100,000 persons and 2.4 cases of viscerotropic disease per 100,000 in persons more than 70 years of age.¹³ The rate of SAEs and neurotropic and viscerotropic diseases was consistently higher among males in all age groups. The incidence of viscerotropic disease in Peru after a focused search for cases was 7.9 cases/100,000 vaccinated persons. Although multiple lines of investigation failed to detect a molecular change in the vaccine, the lot of vaccine involved was subsequently discarded.^{3,14} When a complication is infrequent, it is usually not considered in the differential diagnosis and is easily missed. Failure to report a small number of cases can have a relatively large impact on the reported incidence of rare complications.

Serious adverse effects alter the risk benefit ratio and complicate the decision to vaccinate populations when the risk of yellow fever may be lower than the risk of serious complications.^{15,16} The incidence of yellow fever-associated viscerotropic syndrome has changed the perception of the vaccine from what was perceived as an extremely safe vaccine to one of the least safe vaccines in use.¹⁷

Our patient lived outside the zone of risk for sylvatic yellow fever in Ecuador, but was told to get vaccinated before visiting a country where yellow fever has been eliminated. He died as a result of a vaccine to prevent a disease to which he had not been exposed nor was he going to an area at risk for yellow

fever. Knowledge that the current vaccine for yellow fever has potentially fatal complications, especially in the elderly, should temper the desire to vaccinate persons in areas where yellow fever is no longer endemic, but reemergence is possible and stimulate aggressive vector control in those areas.¹⁴ International vaccine requirements also need to be revised.

Further research in the form of active surveillance of vaccinated populations is needed to determine the true incidence of yellow fever-associated viscerotropic syndrome. Active surveillance needs to be conducted in a zone outside areas of endemic transmission to determine if this vaccine is still one of the least safe vaccines in use. Any serious febrile illness within 10 days of receiving the vaccine should be considered as a possible yellow fever-associated viscerotropic syndrome and aggressively investigated. The 17D strain is also being used as a basis for developing other vaccines.¹⁸ Further research is warranted to understand what components of this vaccine are associated with the viscerotropic syndrome with the hope of eliminating the risk of serious complications of new chimeric vaccines.

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