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Short Report: Suspected Yellow Fever Vaccine-Associated Viscerotropic Adverse Events (1973 and 1978), United States

Thomas P. Monath*
Kleiner Perkins Caufield and Byers, Menlo Park, California

Abstract. Two cases of yellow fever vaccine-associated viscerotropic adverse events (YEL-AVD) were identified by review of correspondence received at the Centers for Disease Control and Prevention (CDC; Ft. Collins, CO). The cases occurred in Indiana and Maryland in 1973 and 1978, respectively. One patient, a 75-year-old man with multi-organ failure died, and the other, a 31-year-old woman, was hospitalized for 14 days. Onset was 3–6 days after vaccination. The illness was characterized by fever, headache, myalgia, gastrointestinal symptoms, hepatic and renal dysfunction, and (in the fatal case), shock and coagulopathy, compatible with YEL-AVD. Liver pathology showed diffuse, spotty necrosis, acidophilic degeneration, Kupffer cell hyperplasia, and microvesicular fat. No virological confirmation was obtained, so that both cases remain classified as "suspect." The 1973 case is the earliest record of YEL-AVD; until now, the earliest known case of YEL-AVD had been in 1975 in Brazil, and most subsequent cases have been reported after 1995.

INTRODUCTION

Yellow fever is a severe mosquito-borne infection characterized by fever, nausea, vomiting, epigastric pain, hepatitis with jaundice, renal failure, hemorrhagic diathesis, and shock, with a case-fatality rate of 20% to 50%. The disease occurs in tropical South America and Africa and has been successfully controlled in many areas by using the live, attenuated yellow fever 17D vaccine developed in 1936 by Theiler and Smith.[1] Yellow fever 17D vaccine evokes protective antibodies in approximately 99% of subjects.[2] Antibodies appear rapidly and are durable, boosters being given every 10 years, although immunity is typically life-long. In the vast majority of people, the vaccine is well tolerated. It causes a mild active infection, low-level viremia between Days 2 and 4 after vaccination, and mild adverse events (fever, myalgia, headache) in 15–20% of subjects.[2]

Safety of the 17D vaccine was first questioned in 2001, when a new syndrome, yellow fever vaccine-associated viscerotropic adverse events (YEL-AVD) was reported.[3–5] The YEL-AVD is a life-threatening acute infection of liver and other vital organs resembling naturally acquired yellow fever disease.[6,7] The pathogenesis of this adverse event involves unchecked replication of vaccine virus in visceral organs. The reported incidence of YEL-AVD approximates 0.4 per 100,000 vaccinations.[8] Both genetic susceptibility caused by defects in innate immunity,[9] and acquired factors, such as advanced age[3,8] and thymectomy,[10] are risk factors for YEL-AVD. In persons ≥ 70 years of age the reported incidence of YEL-AVD is substantially higher than in young persons, 2.3 per 100,000.[8] Cases of YEL-AVD have occurred after vaccination with both the 17D and 17DD substrains of yellow fever vaccine prepared by five different manufacturers. These adverse events are not caused by mutations or other changes in the vaccine virus.[7] Rather, host-specified factors are responsible for the unusual severity of infection in YEL-AVD.[6,7,9]

A total of 56 cases of YEL-AVD (36 fatal, case-fatality rate 64%) have now been identified with the vast majority, 52 cases having occurred since 1996 (Reference 7 and Gershman M, CDC, personal communication, 2009). A retrospective evaluation of virus isolates from Brazilian patients with clinical yellow fever by nucleotide sequence analysis, uncovered a single case of YEL-AVD in 1975.[11] This was the earliest known record of YEL-AVD until now. The recognition of YEL-AVD in 2001, after hundreds of millions of doses of 17D vaccine had been distributed, raised the question whether this rare adverse event was occurring all along but had not been causally associated with vaccination and not reported because of the widely held assumption that the vaccine could not cause full-blown yellow fever.

Going through some old correspondence on yellow fever, the author found information on two intriguing patients in the United States who had experienced syndromes resembling YEL-AVD in 1973 and 1978. The 1973 case is the earliest recorded and is of considerable interest. This brief work describes the clinical features of the two cases. Unfortunately, neither was confirmed virologically.

CASE HISTORIES

Case 1. A 75-year-old white male resident of Indiana received yellow fever 17D vaccination on November 29, 1973, in anticipation of a trip to South America. Six days later he developed flu-like symptoms, with fever, chills, myalgia, nausea, vomiting, mild sore throat, and abdominal pain. He was seen by a physician who noted a temperature of 100°F and prescribed penicillin and an analgesic. The next day, the patient became confused and did not take food or fluids. He was admitted the following day (8 days after vaccination) to Parkview Memorial Hospital, Ft. Wayne, IN. Past history was remarkable for an admission to the hospital 6 weeks earlier with lassitude, pallor, peripheral edema, anemia (hemoglobin 6.6 gm/dL), low serum iron, folate, and B12, diagnosed as pernicious anemia. During that admission he had been noted to have mild hepatosplenomegaly, and a slightly elevated bilirubin of 1.4 mg/dL. On the day of the current admission, the patient was found to be moderately obese, lethargic, acutely ill, and complaining of abdominal pain. The temperature was 98.6°F, pulse 120, and blood pressure 84/48. The face appeared swollen, mucus membranes were dry, the abdomen protuberant and generally tender, with liver and spleen palpable on deep inspiration. Serum urea nitrogen (BUN) was 140 mg/dL,

*Address correspondence to Thomas P. Monath, Kleiner Perkins Caufield and Byers, 2750 Sand Hill Road, Menlo Park, CA 94025. E-mail: tmonath@kpcb.com

glucose 116 mg/dL, total bilirubin 4.4 mg/dL, albumin 2.6 g/dL; alkaline phosphatase, calcium, and phosphorus normal.

On the day after admission, he was admitted to the intensive care unit because of hypotension and deteriorating mental status. The blood pressure was 60/40, temperature 102°F, urine output minimal, and sensorium obtunded. The BUN was 190 mg/dL, creatinine 7.8 mg/dL, bilirubin 5.5 mg/dL (4.2 direct), SGPT 102 U/L, alkaline phosphatase 93 U/L, hematocrit 46.7%, platelets 46,000, white blood cell (WBC) count 13,800/mm^3 with 66% polymorphonuclear cells, 3% bands, 31% lymphocytes. Urinalysis showed 12–15 WBC, 50–60 red blood cells, 3–4 renal epithelial cells, 2 + albumin. The patient was thought to be in acute renal failure, dehydrated, and to have significant hepatic dysfunction. His condition deteriorated, with progression from delirium to coma. His temperature, BUN, creatinine, and WBC remained elevated. Bilirubin increased to 11.2 mg/dL (9.4 direct). He developed a consumption coagulopathy with thrombocytopenia (40,000/mm^3), prolonged prothrombin time (15.4 seconds, 11.4 seconds control) and partial thromoboplastin (66.0 seconds, 31.9 control), and positive fibrin split products, but did not develop overt bleeding. He was treated with corticosteroids, mannitol, heparin, furosamide, and vasopressors. The electrocardiogram (EKG) showed low voltage and peaked T waves in V1–V6. Chest x-ray showed fluid in the right pleural space and congestion. The patient died 3 days after admission (11 days after vaccination). On autopsy, gross anatomical findings included diffuse, focal necrosis of the liver, atrophic gastritis of the stomach, lipid depletion of the adrenal glands, and congestion of both lower lobes of the lung.

A number of experts evaluated the liver histopathology, including Drs. Kamal G. Ishak (Armed Forces Institute of Pathology), Ruth Kirschstein (NIH/FDA), Wilbur G. Downs (Yale Arbovirus Research Unit), Augusto Gast Galvis, head of the yellow fever viscerotomy service, Bogota Colombia, Frederick A. Murphy (Colorado State University), and myself. The findings included focal single cell necrosis, scattered acidophilic degeneration, marked areas of hepatocellular unrest, marked Kupffer cell hypertrophy, cholestasis, and fatty degeneration. The distribution of lesions was not mid-zonal, and for that reason the changes were not considered caused by yellow fever. A fluorescent stain of the frozen liver was negative for yellow fever antigen and fixed liver tissue was examined by electron microscopy and found negative.

Case 2. The patient, a 31-year-old African-American female Maryland resident, was admitted to George Washington University Hospital, Washington, DC in June, 1978, 5 days after having received yellow fever 17D (Merrill National Lot 1873GK) and smallpox vaccinations in anticipation of travel. Three days after vaccination, she had sudden onset of fever to 103°F, myalgia, headache, chills, constipation, nausea, and vomiting, and also had swelling, pain, and stiffness at the site of her yellow fever (but not the smallpox) vaccination. On admission to the hospital, she was acutely ill, with temperature of 105°F, blood pressure 110/60, pulse 84, and respirations 20. Her physical exam was unremarkable. The WBC was 8,400 cells/mm^3 with a striking left shift (91% polymorphonuclear cells, 5% bands, 2% lymphocytes, 2% monocytes) raising the suspicion of a bacterial infection. She was anemic (hematocrit 28.4%). Electrolytes were normal, BUN was slightly elevated but creatinine was normal (0.9 mg/dL). There was 1–2 + protein in urine, mildly elevated amylase, and the aspartate aminotransferase (SGOT) was elevated (107 U/L). Her anemia was believed caused by a long history of metrorrhagia.

Over the next 7 days in the hospital, the patient continued to run a high fever and required a hypothermia blanket to maintain her temperature between 100 and 102°F. She was treated with intravenous hydration and antiemetics. She experienced shaking chills, severe headache, abdominal pain, nausea, and muscle aches, and at times was obtunded. Her liver became palpable and was tender. She was unable to eat until the sixth hospital day. Her liver enzymes rose to a peak SGOT of approximately 800 U/L, SGPT 542 U/L, and LDH 775 U/L. Coagulation tests were normal. She did not become jaundiced, and her maximum total bilirubin was 1.6 mg/dL. Liver scan showed inhomogeneous uptake but was considered "probably normal"; spleen scan and abdominal ultrasound were unremarkable; blood cultures, febrile agglutinins, and mono spot test were negative. Blood obtained 6 days after onset was cultured for virus at the National Instituites of Health (NIH) and found negative. A liver biopsy was performed on the fifth hospital day (10 days after vaccination), and was abnormal, showing significant diffuse microvesicular steatosis, liver cell drop-out, Kupffer cell prominence, scattered Councilman bodies, increased intracellular bile staining, without inflammation or midzonal distribution. The liver was sent to Walter Reed Army Institute for Research and immunofluorescent staining performed with yellow fever antibody; results were negative. The patient improved during the second week after admission, liver enzymes normalized and symptoms dissipated. She was discharged 14 days after admission, with a diagnosis of "Viremia non-defined following yellow fever immunization, with hepatocellular inflammation, prolonged high fever."

During the course of her hospitalization, consultations were held with hospital specialists (gastroenterology, infectious disease) and with outside experts including Drs. Karl Kappus (CDC), Paul Albrecht (NIH/FDA), and William Bancroft (WRAIR). The consultants all noted that "…the illness was consistent with yellow fever…," but that "…there was no previous known vaccine-induced case of yellow fever.…" The microvesicular steatosis in liver biopsy was thought to be unusual and a feature favoring a diagnosis of yellow fever. Two years later, in 1980, Dr. Kappus referred the records on this patient to the present author, who responded that "The case … is fascinating, and I find it hard to believe (it is) unrelated to the 17D yellow fever vaccination. …Failure to isolate yellow fever virus so late in the course means little. To my knowledge, no one has investigated yellow fever vaccinees with febrile 'reactions' to see whether the fever reflects hepatic dysfunction and some residual viscerotropism of the vaccine. This woman might simply be far off on the severe end of the spectrum of febrile reactions with chemical hepatic dysfunction induced by yellow fever vaccine…"

DISCUSSION

These two patients had illnesses clinically consistent with YEL-AVD, with acute onset of illness 3–6 days after vaccination. One case was fatal, in a 75-year-old man who may have had multiple risk factors, including advanced age[8] and autoimmune disease (pernicious anemia). Immune dysregulation associated with autoimmune diseases, including systemic lupus erythematosis[12] and Addison's disease, is a suspected risk factor for YEL-AVD, although this has not been widely recognized and is not yet listed in any product labels. The

physicians responsible for treating Case 1 and (especially) Case 2 suspected that yellow fever vaccine was responsible for illness. Pathological examination of liver tissue obtained post-mortem (Case 1) or on a biopsy (Case 2) was, however, atypical of wild-type yellow fever. In retrospect, a number of histopathological findings were consistent with those seen in some subsequently reported cases of YEL-AVD: diffuse necrosis, eosinophilic degeneration, and microvesicular fatty changes without inflammation. The midzonal distribution of necrosis seen in wild-type disease has been a feature of many, but not all cases of YEL-AVD, and others have a picture of diffuse lesions more like the two cases reported here.[5,12] Death in Case 1 from multi-organ failure occurred 11 days after vaccination, which is typical of fatal cases of YEL-AVD (mean time to death 11.25 days).[7] The clinical and laboratory features of the two cases in 1973 and 1978 were quite consistent with a diagnosis of YEL-AVD. They meet the case definition of suspected cases, because no virological confirmation was made by virus isolation or demonstration of antigen in the liver. The absence of antigen in liver tissue by immunofluorescence is a finding against the diagnosis of YEL-AVD, although there is uncertainty about sensitivity of the methods used. Some recent confirmed cases of YEL-AVD have had very sparse antigen detected by current immunohistochemical methods.[12] Unfortunately, serological responses to yellow fever were not determined in either case; very high antibody levels in some patients with YEL-AVD have been reported, reflecting the high virus load associated with unchecked replication.

Admittedly, these cases of viscerotropic disease temporally associated with yellow fever 17D vaccination could have another etiology. However, there was no evidence in either case for an alternative diagnosis. Many of the reported cases of confirmed YEL-AVD have had a less typical clinical presentation than these two patients. It seems reasonable to accept them as cases of suspect YEL-AVD, with one case occurring in 1973, 2 years before the previously accepted earliest report of this adverse event.[11]

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Author's address: Thomas P. Monath, Kleiner Perkins Caufield and Byers, Menlo Park CA, E-mail: tmonath@kpcb.com.

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